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(54) MATRIX-TYPE TRANSDERMAL PATCH FOR STEROID HORMONES

TRANSDERMALES PFLASTER DES MATRIXTYPS FÜR STEROIDHORMONE

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Description

[0001] The present invention relates to a Transdermal Drug Delivery System (TDDS) (a transdermal patch), to a method for manufacturing such system, and to the use of such system for hormone replacement therapy.

[0002] Estrogens are hormones which are necessary for the sexual development of females at puberty and for the maintenance of the oestrous cycle and secondary sexual characteristics. Estrogens and progesterone induce changes in the reproductive tract and elsewhere in the body of females during the menstrual cycle. Blood estrogen concentrations must be above a certain level for the maintenance of both proliferate and (together with progesterone) secretory phases of the uterine endothelium.

[0003] The menopause occurs when menstruation ceases and indicates the end of a woman's reproductive life; during this phase of a woman's life there is a progressive loss of ovarian functions and there is a decrease in the production of Estradiol and other hormones.

[0004] About 40% of women develop menopausal symptoms serious enough to require medical treatment; the symptoms include mainly vasomotor instability (hot flushes and sweating) and mood and sleep disturbances; during menopause, there is a gradual decrease of bone mass due to a loss of the modulating effect of Estradiol on bone resorption and this process normally leads to osteoporosis. The loss of estrogenic activity changes also the lipid metabolism with a decrease of the ratio of high density lipoprotein (HDL) to low-density lipoprotein (LDL), and this change increases the risk of cardiovascular diseases.

[0005] All these negative effects that can occur in a woman in menopause can be eliminated or at least reduced by an appropriate replacement therapy with estrogen agents, i.e. by the "Hormonal Replacement Therapy" (HRT).

[0006] Oral administration of estrogens as HRT has been extensively used for about 30 years and it was confirmed that, besides the climacteric symptoms, HRT was effective in reducing the death by cardiovascular diseases.

[0007] However, although oral estrogens are effective as HRT, related adverse effects are a problem; a high amount (60 - 90%) of the oral estrogens are converted within the gut wall and liver to inactive metabolites having hepatic adverse effects, therefore relatively high doses of oral estrogens are required to compensate first-pass metabolism.

[0008] Several non-oral formulations of estrogens, which avoid hepatic first-pass effects, have been developed and used as HRT; they include subcutaneous implants, intramuscular injections, vaginal creams and percutaneous gels. However, with such preparations, control of dosage is difficult and patients compliance is poor.

[0009] More recently, transdermal preparations delivering Estradiol at a constant rate have become available. In women with an intact uterus estrogens produce hypertrophy of the endometrium which could provoke cancer. In order to minimize the risk of endometrial hyperplasia and carcinoma of the estrogen therapy in women with an intact uterus the treatment must be opposed intermittently by a progestogen to be associated to the estrogen. The opposition therapy normally is carried out by oral administration of a progestogen like medroxyprogesterone acetate, norethindrone, norethindrone acetate, progesterone, etc. for 10 - 14 days per month.

[0010] A patch delivering both Estradiol and a progestogen is an useful alternative to a method which combines the transdermal administration of Estradiol with the daily oral administration of progestogen. Compliance is likely to be further improved and side effects minimized thanks to a lower progestogen dosage requirement compared with oral therapy.

[0011] Several problems, however, are encountered when including a progestogen in a transdermal patch. Among these one important obstacle is the low, therapeutically uneffective drug release obtained with a transdermal patch of relatively small size; this is due to the poor skin permeation properties of steroid hormones. Another obstacle is the low stability of some progestogens that leads to degradation products.

[0012] In the light of the aforementioned art, there is a need for an optimal transdermal drug delivery system releasing Estradiol and a progestogen through an intact skin resulting in a constant systemic absorption rate.

[0013] Numerous patents refer to the delivery of steroid hormones to the systemic circulation via a transdermal route, and some of them refer to transdermal systems containing Estradiol and Norethindrone Acetate.

[0014] Some inventions refer to the discovery of special matrix formulations containing substances able to reduce the re-crystallization of Estradiol and Norethindrone. Indeed, it is well known for scientists skilled in TDDS that, in order to obtain an adequate release of steroid hormones from transdermal patches, it is necessary to reach in the matrix high concentrations of the hormones (high drug load) or to significantly increase the release area of the patch. The first solution, however, leads quite often to re-crystallization of the hormones during the shelf-life of the product with consequent reduction of the drug release; the second solution often is not acceptable since it reduces patient compliance because of the size of the patch and even could have a negative effect on the adhesivity of the patch during the intended period of use of the product.

[0015] A third possibility to reach an adequate flux from matrix transdermal patches is the inclusion of absorption enhancers (penetration enhancers) in the matrix formulation to generate a high flux of the active compounds when the system is applied to the skin. Typical known enhancers are ethanol, glycerolmonolaurate, DMF, polyethylenglycole monolaurate, etc. Absorption enhancers, however, provoke skin reactions and systemic side effects and this aspect

reduces the ratio efficacy/tolerability of the resulting transdermal systems. They increase the permeability of the stratum corneum of the skin through a modification of the cellular layer, provoking lesions of the skin; they can moreover be absorbed by the skin provoking systemic side effects.

[0016] Another problem known by skilled researchers in TDDS formulations is the low stability of Norethindrone Acetate in acrylic based formulations that leads to degradation products.

[0017] WO 96/03119 (PCT/EP 95/02938) relates to a device for the administration of Estradiol alone or in combination with progestogen(s), encompassing a specific penetration enhancer that achieves elevated transdermal fluxes and optionally an anti-oxidant that achieves good product stability; however, as mentioned above, penetration enhancers can provoke skin reactions.

[0018] WO 94/23707 (PCT EP 94/01231) describes an active substance containing laminated plasters with a carrier and a matrix made of one or two polymers, as well as Vitamin E (tocoferol); tocoferol, however, is not free of potential skin reactions in an occlusive patch that has to remain attached to patient skin for 3-4 days.

[0019] US Patent 4,379,454 refers to a transdermal liquid reservoir patch which contains Estradiol in an alcoholic gel solution; the alcohol contained in the reservoir, however, acts also as an absorption enhancer and can provoke skin reactions.

[0020] WO 9740792 A discloses a matrix type patch for transdermally administering a steroid hormone which comprises a skin permeation enhancing amount of a diethanolamide of a 12 - 18 C fatty acid.

[0021] WO 95/09618 (PCT/EP 94/03269) describes the use of octyldodecanol as crystallization inhibitor in matrix patches containing Estradiol and Norethindrone Acetate.

[0022] DE 44 29 664 refers to a transdermal therapeutic system containing Estradiol and a water absorbing additiv, which is part of the matrix. The system according to this document does not contain a progestogen agent and is said to be applicable to Estradiol only.

[0023] A system for the application of norethisterone acetate is disclosed in DE 195 48 332. It is, however, stated in this document that the addition of an Aerosil to a matrix does not result in a reduced formation of degradation products of norethisterone acetate.

[0024] The object of the invention is the development of a TDDS for HRT releasing Estradiol and at least one progestogen with improved skin permeation of the hormones compared to prior art.

[0025] At the same time the TDDS is to have the following characteristics:

- very simple composition and structure;
- absence of skin penetration enhancers or other compounds which can irritate the skin;
- prolonged and controlled rate of release of the hormones up to 7-days;
- small size;
- good adhesivity onto the skin during the intended period of use;
- easy removal from the skin at the end of the treatment;
- "skin-safe" pressure sensitive adhesive;
- absence of re-crystallization of Estradiol and of the progestogen;
- stability of Estradiol and Norethindrone Acetate without degradation products;
- transparent, cosmetically attractive system;
- good physical stability, i.e. small tendency of creeping of the matrix so that the system can easily be removed from the package.

[0026] It has now been found that it is possible to obtain a TDDS containing steroid hormones that can release high amounts of hormones from relatively small matrix areas without the use of penetration enhancers and avoiding the recrystallization and the degradation of the hormones in the matrix and satisfying all the above characteristics.

[0027] Thus the present invention provides a transdermal patch for the release of Estradiol and at least one progestogen agent through the skin, comprising or consisting of an outer backing foil, a matrix and a protective liner wherein the Estradiol and the progestogen agent(s) are present in the matrix in an over saturated solution, the matrix contains 1 to 5, preferably 1 to 4 wt-% activated SiO_2 and the matrix has a moisture content of less than 0.7 wt.-%. Preferably the matrix has a moisture content of less than 0.5 wt-% and especially preferred is a moisture content of less than 0.4 wt-%. The moisture content refers to the content of free water, that is, the water not adsorbed on or absorbed in the SiO_2.

[0028] In the description and in the claims all percentages refer to weight-% if not indicated otherwise and all contents of the matrix, given in percentages, refer to the weight of the final matrix in the patch, that is, the matrix which comprises the copolymer(s), estradiol, the progestogen agent(s) and optionally further compounds.

[0029] Surprisingly it was found that the hormone release rate from such "moisture-free" matrix-type TDDS containing activated SiO_2 increases significantly with reference to the same non moisture free matrix without using penetration enhancers:

[0030] It was found that moisture-free semi-solid matrix-type TDDS which contain ativated silicon dioxide and steroid hormones in over-saturated solutions have an optimal performance with reference to the release rates of such steroid hormones when applied to human skin. Such unexpected behaviour, although not known with certainty and without intention to be bound to any specific mechanism, is believed to be due to absorption of water from the skin, especially by activated silicon dioxide, when such moisture-free activated silicon dioxide containing systems are applied to human skin and to the consequent decrease of the solubility of the hormones in the matrix. This provokes an increase of the driving force in the system and therefore results in a better flux of the drugs (such surprising characteristics of a matrix containing non water-soluble polymers were not known). It is therefore possible to have a high release of the hormones with TDDS of small release areas (and/or reduced concentration of hormones).

[0031] Moisture-free matrix systems can be obtained by standard manufacturing TDDS processes and concomitant or subsequent treatment of the systems with infrared rays. Thus the energy of water molecules is activated provoking the evaporation of residual water from the matrix at relatively low temperatures that do not provoke degradation of the steroid hormones.

[0032] Moisture-free matrix TDDS which contain activated silicon dioxide in the matrix show an enhanced drug release into the skin. Such surprising indirect enhancing properties in TDDS of moisture-free matrix TDDS containing activated silicon dioxide for steroid hormones were not previously known. In this invention the high rate of delivery is due to a different mechanism compared to that of penetration enhancers utilized in TDDS:

[0033] It is assumed that activated SiO_2 enhances the flux of water from the skin into the matrix thereby increasing the force which drives the hormones out of the matrix so that the flux of Estradiol and the progestogen agent(s) into the skin is/are increased.

[0034] It has been found that a preferred amount of SiO_2 in the matrix lies in the range from 2.5 to 3.5 wt-%; and an amount of about 3 wt-% SiO_2 is especially preferred. An amount above 5 wt-% is detrimental to the flux of the active ingredients in the matrix in that the concentration of the ingredients in the matrix must be lowered when the content of SiO_2 is increased. An amount of less than 1 wt-% SiO_2 will not attract a sufficient amount of water to increase the flux of the active ingredients.

[0035] SiO_2 can be activated according to the present invention by irradiating the patch - with or preferably without the release liner being applied - with an IR-source. At the same time irradiation of the matrix reduces its water content to the required level.

[0036] The matrix systems according to the present invention can thus be obtained by standard manufacturing TDDS processes and concomitant or subsequent treatment of the systems with infrared rays.

[0037] By irradiation the energy of water molecules is probably activated provoking the evaporation of residual water from the matrix and inter alia the evaporation of absorbed water of SiO_2 at relatively low temperatures.

[0038] Activated silicon dioxide can be prepared by irradiating silicon dioxide (like an Aerosil, especially Aerosil 380) with an IR source.

[0039] It has been shown that the results are particularly adequate when irradiating the matrix of the patch including the silicon dioxide with infrared rays having a wavelength of 1 to 100 µm, preferably of 1 and 10 µm, for 1 to 10 minutes, preferably for 1 to 5 minutes with an incandescent filament lamp of an adequate power (Watt) at a distance of 20 to 40 cm generating a temperature of 40 to 120 °C, preferably of 60 to 90 °C. Preferably the lamp(s) have an active power of 100 to 3000 Watt.

[0040] The inclusion in the matrix of activated, preferably colloidal, silicon dioxide moreover contributes to maintain the system anhydrous. This condition of the matrix system probably reduces the solubility of the hormones in the patch and increases the flux.

[0041] The most important feature of this invention is the use of a moisture-free matrix containing activated silicon dioxide which allows for a high flux of drugs into the skin from small patches without skin penetration (rate) enhancers.

[0042] The at least one pressure sensitive adhesive used for the matrix of this invention is selected from a group of vinylacetate containing acrylate copolymers; specifically the matrix consists of one, two or more pressure sensitive adhesive copolymers, obtainable by the radical copolymerisation of:

a) 2-ethylhexylacrylate (2-EHA) preferably in an amount of 44% to 80%, preferably 48% to 75% and especially 50% to 68%.
b) Hydroxyethyl-acrylate (HEA) preferably in an amount of 2.5% and 9.7%, preferably 4.0% to 5.0%;
c) vinylacetate (VA) preferably in an amount of 8% to 48.2%, preferably 20% to 26%;
d) glycidylmethacylate (GMA), preferably in an amount of 0.01 to 0.3%, preferably of 0.1% to 0.2%;
e) and in the presence of other substances in quantities of up to 5%, all percentages being based on the weight of the matrix of the final patch.

[0043] Among several progestogens, Norethindrone Acetate is preferred because it is effective at low doses and therefore can be formulated in TDDS and because it has some additional effects, e.g. on libido, that are absent in other

progestogens like progesterone and medroxyprogesterone.

[0044] In the described matrix Estradiol (as hemihydrate) and the progestogen agent(s) like Norethindrone Acetate can be maintained in high concentration. Thus the matrix can have an Estradiol content of 1.0 to 3%, preferably of 1.5 to 2.5 % and especially of 1,8 to 2.4% and a content of at least one progestogen agent like Norethindrone Acetate of 2 to 12%, preferably of 4 to 11% and especially of 5 to 9%. In these concentrations, Estradiol and the progestogen agent like Norethindrone Acetate, although being in a supersaturated (= over saturated) solid solution in this matrix, do not re-crystallize and are maintained in a condition that confers to the steroid hormones a high thermodynamic activity.

[0045] The matrix can preferably contain 1 to 5 wt-% of silicon dioxide to contribute to the maintanance of an anhydrous state in the matrix and to provoke absorption of water from the skin when the patch is applied.

[0046] In order to eventually improve the matrix characteristics, it is possible to include in the matrix small amounts of up to 4%, preferably of up to 3 % of other compounds having e.g. a solubilizing effect on the active ingredients, or avoiding re-crystallization thereof or having drying activities or acting as preservatives or antioxidants, etc.

[0047] Preferably the thickness of the matrix should be kept low enough so that it can be dried during the drying step of the manufacturing process and that the solvent content, including the moisture content can be reduced to a minimum.

[0048] Thus the matrix preferably has a thickness of 20 to 100 μm, more preferred of 30 (or 40) to 80 μm and especially of 50 to 70 μm.

[0049] The patch according to the present invention can be a laminated composite with a backing foil that is substantially impermeable to the drugs and the adhesive copolymer(s) of the matrix and supports the matrix.

[0050] The backing foil can be made from one or more materials selected from the group consisting of polyester, polyurethane, polyethylene, polyethylene terephtalate, polypropylene and polyvinyl chloride materials; and the side of the backing foil not facing the matrix can be lacquered, preferably by a lacquer comprising epoxy resins or polyaminoamido resins containing opacifying agents and it can have a thickness of 10 to 45 (or 50) μm and preferably 12 (or 15) to 30 μm.

[0051] Thus the backing foil or layer according to the present invention can be an occlusive or a transparent material, preferably a transparent polyester material such as polyethylene terephthalate.

[0052] For better handling during its production such material can be lacquered on the side not in contact with the matrix with an epoxy resin containing opacifying agents.

[0053] In order to protect the matrix during storage a protective (release) liner is used; such release liner can be impermeable to the active ingredients and the pressure sensitive adhesive(s) and should be easily removable by the patient before the application of the patch.

[0054] The release liner can be made of at least one foil of paper, polyester, polyethylene, polypropylene, polyethylene terephtalate (PET) or polyvinylchloride. It is preferably coated, to reach the requested release strength, on one or both sides with a silicon system or fluoropolymer coating blend. The optimum thickness for an appropriate rigidity of the release liner is 50 to 150 (or 200) μm and preferably between 60 (or 80) to 120 (or 150) μm.

[0055] In order to facilitate its detachment from the patch, a pull-off tag can be cut in the release liner and, where requested, an appropriate profile ring is stamped on the liner in order to maintain a distance from the backing foil to the internal wall of a pouch (sachet) material into which the patch can be sealed, so that the profile ring prevents the sticking of the patch on the internal wall of the sachets. The sachet can comprise a humidity impermeable foil, preferably a multi-layered foil, which is preferably made of sheets of aluminium, paper, polyethylene or polyvinylchloride, especially Surlyn^{R}.

[0056] To maintain the matrix "moisture-free" (to allow a high flux of the hormones) the sachets can contain as a precaution a desiccant such as silica gel, sodium sulfate, calcium sulfate, calcium carbonate dihydrate or a mixture thereof.

[0057] Preferably the transdermal patch according to the invention has a circular or oval shape or a square shape with round edges, and/or a release area of 5 to 60 cm^2 and preferably 8 to 40 cm^2.

[0058] According to the present invention there is also disclosed the use of a transdermal patch according to the invention for hormonal replacement therapy.

Examples

[0059] The description of the present invention and the manufacture of the relevant TDDS delivering Estradiol and a progestogen agent like Norethindrone Acetate are illustrated by the following examples:

Example 1

Preparation of the adhesive mixture with ingredients:

[0060] 12.05 kg of a vinylacetate-acrylate copolymer solution having a solid content of about 51% are homogenized under stirring together with 0.1621 kg of Estradiol Hemihydrate and 0.6055 kg of Norethindrone Acetate; the suspension is transferred into 6.96 kg of a 50 : 50 mixture of Ethyl Acetate and Ethanol (these solvent materials were later removed during drying) and 0.2098 kg of Aerosil 380 are added; the mixture is then maintained under stirring for 24 hours at room temperature until a homogenous mass is obtained.

[0061] The ratio of the monomers used to prepare the vinylacetate-acrylate copolymer of the (final) matrix obtained are as follows:

- 2-ethylhexyl acrylate: 58.67 %
- vinylacetate: . 22.43 %
- 2-hydroxyethylacrilate: 4.31 %
- glycidyl metacrylate: 0.13 %

Preparation of the medicated laminate:

[0062] The drug solvent polymer mixture was then cast to a thickness of about 60 micrometers on a polyester film (backing foil) to obtain after drying a matrix having a weight of 60 g/m^2.

[0063] Drying of the medicated laminate is carried out at a temperature between 35 and 95°C and this leads to a composition of 0.135 mg of Estradiol and 0.520 mg of Norethindrone Acetate per cm^2 of the dried matrix.

[0064] At this temperature the matrix cannot be dried completely and the water content deriving from the materials and solvents used, from the environment and also from the Estradiol Hemihydrate used cannot be eliminated. The medicated laminate, after drying, is treated for about 2 minutes with an IR lamp able to eliminate the water and to activate the silicon dioxide at a temperature of less than 100 °C. In this way it is possible to avoid degradation of the hormones and especially of Norethindrone Acetate that can occur if the matrix is treated at high temperatures.

[0065] After drying and IR lamp treatment, the release liner , i.e. a polyester foil of 80 µm thickness, coated with a fluoropolymer, is stuck on the matrix to form the final medicated laminate.

Punching of the transdermal patch:

[0066] Circular or oval shapes or square shapes with round edges having a release area of 8 to 40 cm^2 are punched from the medicated foil to form the final transdermal patches; the size is decided according to the requested release rate of Estradiol and Norethindrone Acetate.

[0067] A not-to-scale cross-sectional view and a front view of a transdermal patch obtained according to this invention is given in Figure 1.

[0068] In Figur 1

(1) is a lacquered backing foil
(2) is a drug containing adhesive matrix
(3) is a protective liner, and
(4) is a profile ring.

Sealing into the pouches:

[0069] Each transdermal patch is sealed into a pouch not permeable to moisture and composed of a 4-layered material made by paper, polyethylene foil, aluminium foil and surlyn ionomer foil. To maintain the matrix of the TDDS moisture-free, a desiccant like calcium carbonate dihydrate may be included in the pouch.

Comparative Example 2 (reference preparation)

Preparation of the medicated laminate:

[0070] Proceed as in Example 1.

[0071] All the remaining steps are as in Example 1; in this example, however, the medicated laminate is not irradiated with the infrared lamp(s).

Quantitative assay of (free) water in transdermal patches

[0072] The transdermal patches resulting from each of the preparations described have been tested with the Karl-Fischer method in order to quantify the (free) water content in the matrix of the systems:

[0073] The (free) water content in the transdermal patches can be driven off in a tube furnace at a certain temperature. It can then be transferred to a Karl-Fischer titration cell by an inert gas where it is titrated by a Coulometric method with specific reagents. A suitable arrangement for such a technique is depicted in Figure 2.

[0074] A constant flow of air is achieved by regulating valve R and monitoring the air flow using the flowmeter D. The air is then dried in the drying towers T before being passed over the heated sample (P) (a patch or portion of patch) into the titration cell Z depicted in Figure 3.

[0075] In Figure 3

(1) is an inner burette,
(2) is a catholyte,
(3) is a cathode,
(4) is a membrane,
(5) is an anode,
(6) is a detection electrode (double platinum pin electrode),
(7) is a titration vessel,
(8) is an anolyte, and
(9) is a rotor.

[0076] In this assay the following devices, reagents and experimental conditions can be used:

1. Apparatus

The specific apparatus used is the METTLER DO 337 Drying Oven coupled with the METTLER DL 37 KF Coulometer.

2. Reagents used in the titration cell

- Hydranal® - Coulomat AG, art. 34836 (in compartment A)
- Hydranal® - Coulomat CG, art. 34840 (in compartment C) (supplier Riedel-de-Haën, D- 30918 Seelze, Germany)

3. Experimental conditions

The experimental conditions used for determining the (free) water content in the matrix of the transdermal patches were:

- Flow of air: 300 ml/min
- Temperature of the furnace: 80 °C
- Size of the patch sample: 20 cm^2
- Time of exposure of sample to 80 °C: 15 minutes

[0077] The system can detect from 100 to 3000 µg of (free) water equivalent to a percentage of water in the matrix of the present invention ranging approximately from 0.1 to 2.5 %.

[0078] With this system the content of (free) water in the matrix is determined, the amount of water adsorbed on or absorbed by the silicon dioxide cannot be determined thereby.

[0079] For each of the products according to the two examples five units have been tested and the results are shown below:

Table 1:

Moisture content in Estradiol - NETA patches		
Product	*1*	*C-2*
Moisture wt.-%	0.15	0.85
	0.13	0.81
	0.18	0.72
	0.15	0.78
	0.16	0.75
Average	0.15	0.78
SD	0.0013	0.0507

[0080] A comparative study of the flux trough human cadaver skin, carried out with the modified Franz diffusion cell, is presented in the following tables and graphs. It can be seen that the systems of the present invention exhibit elevated skin fluxes of Estradiol and Norethindrone Acetate (NETA) compared to the reference system.

Table 2 and Table 3: in-vitro release (human skin) of Estradiol and NETA

Cumulative mean value: release of Estradiol and NETA

Release of Estradiol (µg/cm^2, n=3)

Product	8 h	24 h	48 h	72 h	flux.µg/cm^2/h
1	0.310	1.319	2.412	2.932	0.049 s.d.±0.0071
C-2	0.217	0.797	1.424	2.054	0.031 s.d.±0.0021

Release of NETA (µg/cm^2, n=3)

Product	8 h	24 h	48 h	72 h	flux.µg/cm^2/h
1	1.118	2.482	4.395	5.481	0.090 s.d±0.0014
C-2	0.359	1.352	2.512	3.870	0.054 s.d±0.0020

Claims

1. A transdermal patch for the release of Estradiol and at least one progestogen agent through the skin, comprising or consisting of an outer backing foil, a matrix and a protective liner wherein

   a) the Estradiol and the progestogen agent(s) are present in the matrix in an oversaturated solution,
   b) the matrix contains 1 to 4 wt% activated SiO_2 , and
   c) the matrix has a moisture content of less than 0.7 wt.-%.

2. A transdermal patch according to claim 1 **characterized in that** the matrix has a moisture content of less than 0.5 wt.-%.

3. A transdermal patch according to claim 1 or 2, **characterized in that** the matrix contains 2,5 to 3,5 wt% SiO_2.

4. A transdermal patch according to any of the preceding claims **characterized in that** the SiO_2 is activated by irradiation with an infrared source.

5. A transdermal patch according to any of the preceding claims **characterized in that** it is free of penetration enhancers.

6. A transdermal patch according to any of the preceding claims **characterized in that** the matrix consists of one, two or more pressure sensitive adhesive copolymers obtainable by radical copolymerization of:

   - 2-ethylhexyl acrylate,
   - hydroxyethyl acrylate,
   - vinylacetate and
   - glycidyl methacrylate,

   optionally in the presence of **other substances** in quantities of up to 0.5 wt.-%, based on the weight of the matrix.

7. A transdermal patch according to claim 6 **characterized in that** the monomers are used in the following amounts:

   - 2-ethylhexyl acrylate is used in an amount of 44 to 80 wt.-%, preferably 48 to 75 wt.-% and especially 50 to 68 wt.-%,
   - hydroxyethyl acrylate is used in an amount of 2.5 to 9.7 wt.-%, preferably 4.0 to 5.0 wt.-%,
   - vinylacetate is used in an amount of 8 to 48.2 wt.-%, preferably 20 to 26 wt.-%, and
   - glycidyl methacrylate is used in an amount of 0.01 to 0.3 wt.-%, preferably 0.1 to 0.2 wt.-%, all percentages being based on the weight of the matrix.

8. A transdermal patch according to any of the preceding claims **characterized in that** the matrix has a thickness of 20 to 100 µm, preferably of 40 to 80 µm.

9. A transdermal patch according to any of the preceding claims, **characterized in that** the matrix has an Estradiol content of 1 to 3 wt.-%, preferably 1.5 to 2.5 wt.-% and especially 1.8 to 2.4 wt.-%.

10. A transdermal patch according to any of the preceding claims, **characterized in that** the matrix has a progestogen agent content of 2 to 12 wt.-%, preferably 4 to 11 wt.-% and especially 5 to 9 wt.-%.

11. A transdermal patch according to any of the preceding claims, **characterized in that** the matrix has a content of other compounds of up to 4 wt.-%.

12. A transdermal patch according to any of the preceding claims **characterized in that** the progestogen agent is norethindrone acetate.

13. A transdermal patch according to any of the preceding claims, **characterized in that**

- the backing foil consists of a material impermeable to the drugs and to the adhesive copolymer(s), preferably made from one or more materials selected from the group consisting of polyester, polyurethane, polyethylene, polyethylene terephtalate, polypropylene and polyvinyl chloride materials; and/or
- the side of the backing foil not facing the matrix is lacquered, preferably by a lacquer comprising epoxy resins and/or polyaminoamido resins containing opacifying agents and/or
- the backing foil has a thickness of 10 to 50 µm and preferably 12 to 30 µm.

14. A transdermal patch according to any of the preceding claims, **characterized in that** the patch comprises a removable protective liner

- made of at least one foil of paper, polyester, polyethylene, polyethylene terephtalate, polypropylene or polyvinylchloride or mixtures thereof, preferably coated with silicone or a fluoropolymer on one or both sides, and/or
- having a thickness of 50 to 200 µm and preferably 80 to 150 µm; and/or
- being provided with a cut-off tag and a stamped profile ring.

15. A transdermal patch according to any of the preceding claims, **characterized by** a circular or oval shape or a square shape with round edges, and/or a release area of 5 to 60 cm^2 and preferably 8 to 40 cm^2.

16. A transdermal patch according to any of the preceding claims, **characterized in that** it is sealed in a sachet comprising a humidity impermeable foil, preferably a multi-layered foil, which is preferably made of sheets of aluminium, paper, polyethylene or polyvinylchloride, especially ionomer foil.

17. A transdermal patch according to claim 16, **characterized in that** the sachet contains a desiccant like silica gel, sodium sulfate, calcium sulfate, calcium carbonate dihydrate or a mixture thereof.

18. A process for the production of a transdermal patch according to any of the preceding claims **characterized in that**

a) Estradiol and at least one progestogen agent are mixed with a copolymer solution,
b) a silicon dioxide is added to the mixture,
c) the mixture is applied to a backing layer to form a laminate,
d) the laminate is dried at a temperature from 35 to 95 °C,
e) the laminate is irradiated with IR-rays, and
f) the laminate is covered with a protective liner.

19. Use of a transdermal patch according to any of claims 1 to 17 for the manufacture of a medicament for hormonal replacement therapy.

Patentansprüche

1. Transdermales Pflaster für die Abgabe von Östradiol und mindestens eines gestagenen Mittels durch die Haut, umfassend oder bestehend aus einer äußeren Trägerfolie, einer Matrix und einer Schutzfolie, wobei

a) das Östradiol und das (die) gestagene(n) Mittel in der Matrix in einer übersättigten Lösung vorliegen,
b) die Matrix 1 bis 4 Gew.-% aktiviertes SiO_2 enthält, und
c) die Matrix einen Feuchtigkeitsgehalt von weniger als 0,7 Gew.-% besitzt.

2. Transdermales Pflaster nach Anspruch 1, **dadurch gekennzeichnet, daß** die Matrix einen Feuchtigkeitsgehalt von weniger als 0,5 Gew.-% besitzt.

3. Transdermales Pflaster nach Anspruch 1 oder 2, **dadurch gekennzeichnet, daß** die Matrix 2,5 bis 3,5 Gew.-% SiO_2 enthält.

4. Transdermales Pflaster nach einem der vorausgehenden Ansprüche, **dadurch gekennzeichnet, daß** das SiO_2

durch Bestrahlung mit einer Quelle für infrarote Strahlung aktiviert wird.

5. Transdermales Pflaster nach einem der vorausgehenden Ansprüche, **dadurch gekennzeichnet, daß** es frei von Penetrationsverstärkern ist.

6. Transdermales Pflaster nach einem der vorausgehenden Ansprüche, **dadurch gekennzeichnet, daß** die Matrix aus einem, zwei oder mehreren druckempfindlichen, klebenden Copolymeren besteht, erhältlich durch radikalische Copolymerisation von:

- 2-Ethylhexyl-acrylat,
- Hydroxyethyl-acrylat,
- Vinylacetat und
- Glycidyl-methacrylat,

gegebenenfalls in Gegenwart von anderen Substanzen in Mengen von bis zu 0,5 Gew.-%, bezogen auf das Gewicht der Matrix.

7. Transdermales Pflaster nach Anspruch 6, **dadurch gekennzeichnet, daß** die Monomere in folgenden Mengen eingesetzt werden:

- 2-Ethylhexyl-acrylat wird in einer Menge von 44 bis 80 Gew.-% verwendet, vorzugsweise 48 bis 75 Gew.-% und besonders 50 bis 68 Gew.-%,
- Hydroxyethyl-acrylat wird in einer Menge von 2,5 bis 9,7 Gew.-% eingesetzt, vorzugsweise 4,0 bis 5,0 Gew.-%,
- Vinylacetat wird in einer Menge von 8 bis 48,2 Gew.-% eingesetzt, vorzugsweise 20 bis 26 Gew.-%, und
- Glycidyl-methacrylat wird in einer Menge von 0,01 bis 0,3 Gew.-% eingesetzt, vorzugsweise 0,1 bis 0,2 Gew.-%, alle Prozentangaben beziehen sich auf das Gewicht der Matrix.

8. Transdermales Pflaster nach einem der vorausgehenden Ansprüche, **dadurch gekennzeichnet, daß** die Matrix eine Dicke von 20 bis 100 µm besitzt, vorzugsweise von 40 bis 80 µm.

9. Transdermales Pflaster nach einem der vorausgehenden Ansprüche, **dadurch gekennzeichnet, daß** die Matrix einen Östradiolgehalt von 1 bis 3 Gew.-%, vorzugsweise von 1,5 bis 2,5 Gew.-%, und besonders von 1,8 bis 2,4 Gew.-% besitzt.

10. Transdermales Pflaster nach einem der vorausgehenden Ansprüche, **dadurch gekennzeichnet, daß** die Matrix einen Gehalt an einem gestagenen Mittel von 2 bis 12 Gew.-%, vorzugsweise von 4 bis 11 Gew.-%, und besonders von 5 bis 9 Gew.-% besitzt.

11. Transdermales Pflaster nach einem der vorausgehenden Ansprüche, **dadurch gekennzeichnet, daß** die Matrix einen Gehalt an weiteren Verbindungen von bis zu 4 Gew.-% besitzt.

12. Transdermales Pflaster nach einem der vorausgehenden Ansprüche, **dadurch gekennzeichnet, daß** das gestagene Mittel Norethindronacetat ist.

13. Transdermales Pflaster nach einem der vorausgehenden Ansprüche, **dadurch gekennzeichnet, daß**

- die Trägerfolie aus einem Material besteht, das undurchlässig für die Arzneimittel und das (die) klebende(n) Copolymer(e) ist, vorzugsweise aus einem oder mehreren Materialien hergestellt ist, die aus der Gruppe ausgewählt werden, welche aus Polyester-, Polyurethan-, Polyethylen-, Polyethylenterephthalat-, Polypropylen- und Polyvinylchlorid-Materialien besteht; und/oder

- die Seite der Trägerfolie, welche nicht der Matrix zugewandt ist, lackiert ist, vorzugsweise mit einem Lack, umfassend ein Epoxidharz und/oder Polyaminoamidoharze, die lichtundurchlässige Mittel enthalten, und/oder

- die Trägerfolie eine Dicke von 10 bis 50 µm und vorzugsweise von 12 bis 30 µm besitzt.

14. Transdermales Pflaster nach einem der vorausgehenden Ansprüche, **dadurch gekennzeichnet, daß** das Pflaster eine abziehbare Schutzfolie umfaßt,

- welche aus mindestens einer Folie aus Papier, Polyester, Polyethylen, Polyethylenterephthalat, Polypropylen oder Polyvinylchlorid oder deren Mischungen besteht, vorzugsweise mit Silicon oder einem Fluorpolymer auf einer oder beiden Seiten beschichtet ist, und/oder
- eine Dicke von 50 bis 200 µm und vorzugsweise von 80 bis 150 µm besitzt; und/oder
- mit einem abgeschnittenen losen Ende und einem aufgeprägten Profilring versehen ist.

15. Transdermales Pflaster nach einem der vorausgehenden Ansprüche, **gekennzeichnet durch** eine kreisförmige oder ovale Form oder eine quadratische Form mit gerundeten Ecken und/oder einer Abgabefläche von 5 bis 60 cm^2, und vorzugsweise von 8 bis 40 cm^2.

16. Transdermales Pflaster nach einem der vorausgehenden Ansprüche, **dadurch gekennzeichnet, daß** es in einen Verpackungsbeutel eingeschlossen ist, umfassend eine feuchtigkeitsundurchlässige Folie, vorzugsweise eine multibeschichtete Folie, welche vorzugsweise aus Blättern von Aluminium, Papier, Polyethylen oder Polyvinylchlorid, insbesondere Ionomerfolien hergestellt ist.

17. Transdermales Pflaster nach Anspruch 16, **dadurch gekennzeichnet, daß** der Verpackungsbeutel ein Trocknungsmittel wie Silicagel, Natriumsulfat, Calciumsulfat, Calciumcarbonat-Dihydrat oder deren Mischungen enthält.

18. Verfahren zur Herstellung eines transdermalen Pflasters nach einem der vorausgehenden Ansprüche, **dadurch gekennzeichnet, daß**

    a) Östradiol und mindestens ein gestagenes Mittel mit einer Copolymerlösung vermischt werden,
    b) ein Siliciumdioxid zur Mischung hinzugegeben wird,
    c) die Mischung auf eine Trägerschicht aufgebracht wird, um eine Beschichtung zu bilden,
    d) die Beschichtung bei einer Temperatur von 35 bis 95° C getrocknet wird,
    e) die Beschichtung mit infraroten Strahlen bestrahlt wird, und
    f) die Beschichtung mit einer Schutzfolie bedeckt wird.

19. Verwendung eines transdermalen Pflasters nach einem der Ansprüche 1 bis 17 zur Herstellung eines Medikaments für die Hormonersatztherapie.

Revendications

1. Pansement transdermique pour la libération d'estradiol et d'au moins un agent progestogène à travers la peau, qui comprend ou qui est constituée d'une feuille de renforcement externe, d'une matrice et d'un revêtement protecteur, pansement pour lequelle:

    a) l'estradiol et le ou les agent(s) progestogènes sont présents dans la matrice sous la forme d'une solution sursaturée,

    b) la matrice contient 1 à 4 % en poids de SiO_2 activée, et

    c) la matrice a une teneur en humidité inférieure à 0,7 % en poids.

2. Pansement transdermique selon la revendication 1, **caractérisée en ce que** la matrice a une teneur en humidité inférieure à 0,5 % en poids.

3. Pansement transdermique selon la revendication 1 ou 2, **caractérisée en ce que** la matrice contient 2,5 à 3,5 % en poids de SiO_2.

4. Pansement transdermique selon l'une quelconque des revendications précédentes, **caractérisée en ce que** la silice SiO_2 est activée par exposition à une source de rayons infrarouges.

5. Pansement transdermique selon l'une quelconque des revendications précédentes, **caractérisée en ce qu'**elle est exempte d'agents facilitant la pénétration.

6. Pansement transdermique selon l'une quelconque des revendications précédentes, **caractérisée en ce que** la matrice est constituée d'un, de deux ou de plus de deux copolymères adhésifs sensibles à la pression, que l'on peut obtenir par copolymérisation radicalaire d'acrylate de 2-éthylhexyle, d'acrylate d'hydroxyéthyle, d'acétate de vinyle et de méthacrylate de glycidyle, éventuellement en présence d'autres substances en une proportion atteignant au plus 0,5 % en poids par rapport au poids de la matrice.

7. Pansement transdermique selon la revendication 6, **caractérisée en ce que** l'on utilise les monomères dans les proportions suivantes :

   - l'acrylate de 2-éthylhexyle est utilisé en une proportion de 44 à 80 % en poids, de préférence de 48 à 75 % en poids et en particulier de 50 à 68 % en poids,
   - l'acrylate d'hydroxyéthyle est utilisé en une proportion de 2,5 à 9,7 % en poids, de préférence de 4,0 à 5,0 % en poids,
   - l'acétate de vinyle est utilisé en une proportion de 8 à 48,2 % en poids, de préférence de 20 à 26 % en poids, et
   - le méthacrylate de glycidyle est utilisé en une proportion de 0,01 à 0,3 % en poids, de préférence de 0,1 A 0,2 % en poids,

   tous les pourcentages étant basés sur le poids de la matrice.

8. Pansement transdermique selon l'une quelconque des revendications précédentes, **caractérisée en ce que** la matrice a une épaisseur de 20 à 100 µm, de préférence de 40 à 80 µm.

9. Pansement transdermique selon l'une quelconque des revendications précédentes, **caractérisée en ce que** la matrice a une teneur en estradiol de 1 à 3 % en poids, de préférence de 1,5 à 2,5 % en poids et en particulier de 1,8 à 2,4 % en poids.

10. Pansement transdermique selon l'une quelconque des revendications précédentes, **caractérisée en ce que** la matrice a une teneur en agent progestogène de 2 à 12 % en poids, de préférence de 4 à 11 % en poids et en particulier de 5 à 9 % en poids.

11. Pansement transdermique selon l'une quelconque des revendications précédentes, **caractérisée en ce que** la matrice a une teneur en autres composés de jusqu'à 4 % en poids.

12. Pansement transdermique selon l'une quelconque des revendications précédentes, **caractérisée en ce que** l'agent progestogène est l'acétate de noréthindrone.

13. Pansement transdermique selon l'une quelconque des revendications précédentes, **caractérisée en ce que**

   - la feuille de renforcement est constituée d'une matière imperméable aux médicaments et aux copolymères adhésifs, faite de préférence d'un ou plusieurs produits choisis parmi les polyesters, les polyuréthanes, les polyéthylènes, les poly(téréphtalate d'éthylène), les polypropylènes et les polychlorures de vinyle, et/ou
   - le côté de la feuille de renforcement qui ne fait pas face à la matrice, est laqué, de préférence au moyen d'une laque comprenant des résines époxy et/ou des résines polyaminoamido contenant des agents opacifiants, et/ou
   - la feuille de renforcement a une épaisseur de 10 à 50 µm, de préférence de 12 à 30 µm.

14. Pansement transdermique selon l'une quelconque des revendications précédentes, **caractérisée en ce qu'**il comprend un revêtement protecteur ôtable, constitué d'au moins une feuille de papier, de polyester, de polyéthylène, de poly(téréphtalate d'éthylène), de polypropylène, de polychlorure de vinyle ou d'un mélange de ces produits, revêtue de préférence de silicone ou d'un polymère fluoré sur une face ou les deux faces, et/ou ayant une épaisseur de 50 à 200 µm, de préférence de 80 à 150 µm, et/ou muni d'une languette de détachage et d'un anneau à profil imprimé.

15. Pansement transdermique selon l'une quelconque des revendications précédentes, **caractérisée par** une forme circulaire, une forme ovale ou une forme carrée à angles arrondis, et/ou par une surface de libération de 5 à 60 cm^2. de préférence de 8 à 40 cm^2.

16. Pansement transdermique selon l'une quelconque des revendications précédentes, **caractérisée en ce qu'**elle est enfermée hermétiquement dans un sachet comprenant une feuille imperméable à l'humidité, de préférence une feuille multicouche, qui est constituée de préférence de feuilles d'aluminium, de papier, de polyéthylène, de poly(chlorure de vinyle) et en particulier d'ionomères.

17. Pansement transdermique selon la revendication 16, **caractérisée en ce que** le sachet contient un desséchant comme du gel de silice, du sulfate de sodium, du sulfate de calcium, du carbonate de calcium dihydraté ou un mélange de ces produits.

18. Procédé de production d'un pansement transdermique selon l'une quelconque des revendications précédentes, **caractérisé en ce que** :

a) on mélange de l'estradiol et au moins un agent progestogène à une solution de copolymère,

b) on ajoute du dioxyde de silicium au mélange,

c) on applique le mélange sur une couche de renforcement pour former un stratifié,

d) on sèche le stratifié à une température de 35 à 95 °C,

e) on irradie le stratifié avec des rayons infrarouges, et

f) on recouvre le stratifié avec un revêtement protecteur.

19. Utilisation d'un pansement transdermique selon l'une quelconque des revendications 1 à 17 pour la fabrication d'un médicament destiné à une thérapie de remplacement hormonal.

Fig. 1:

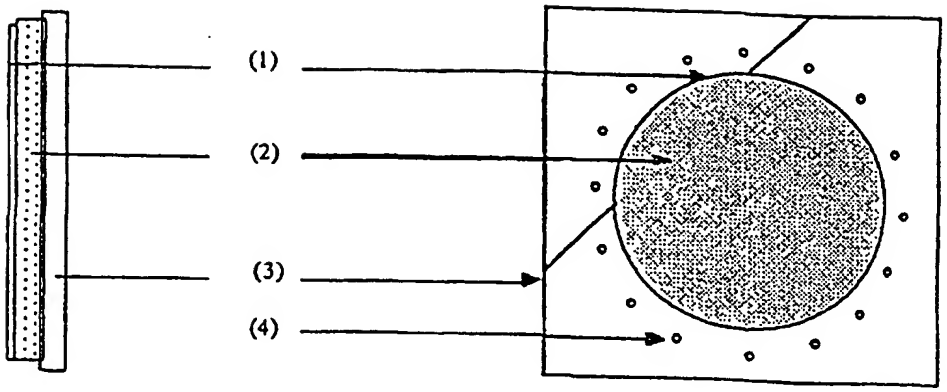
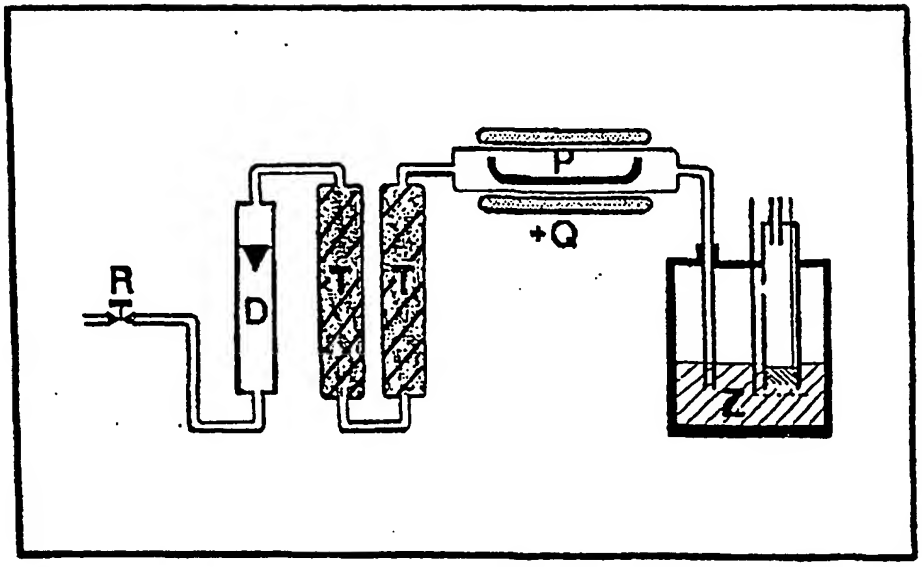


Fig. 2:



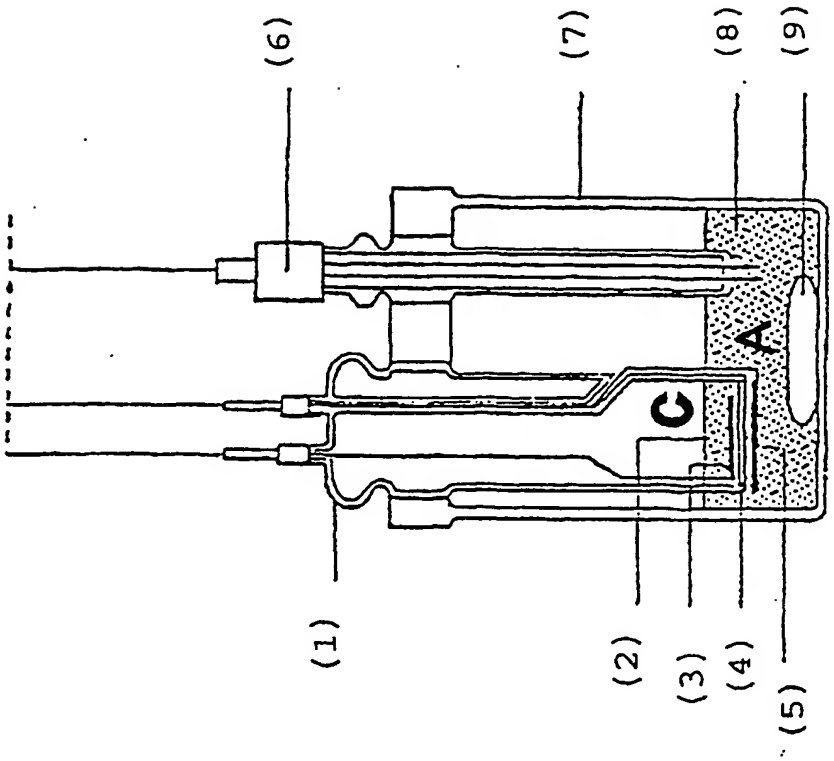


Fig. 3:

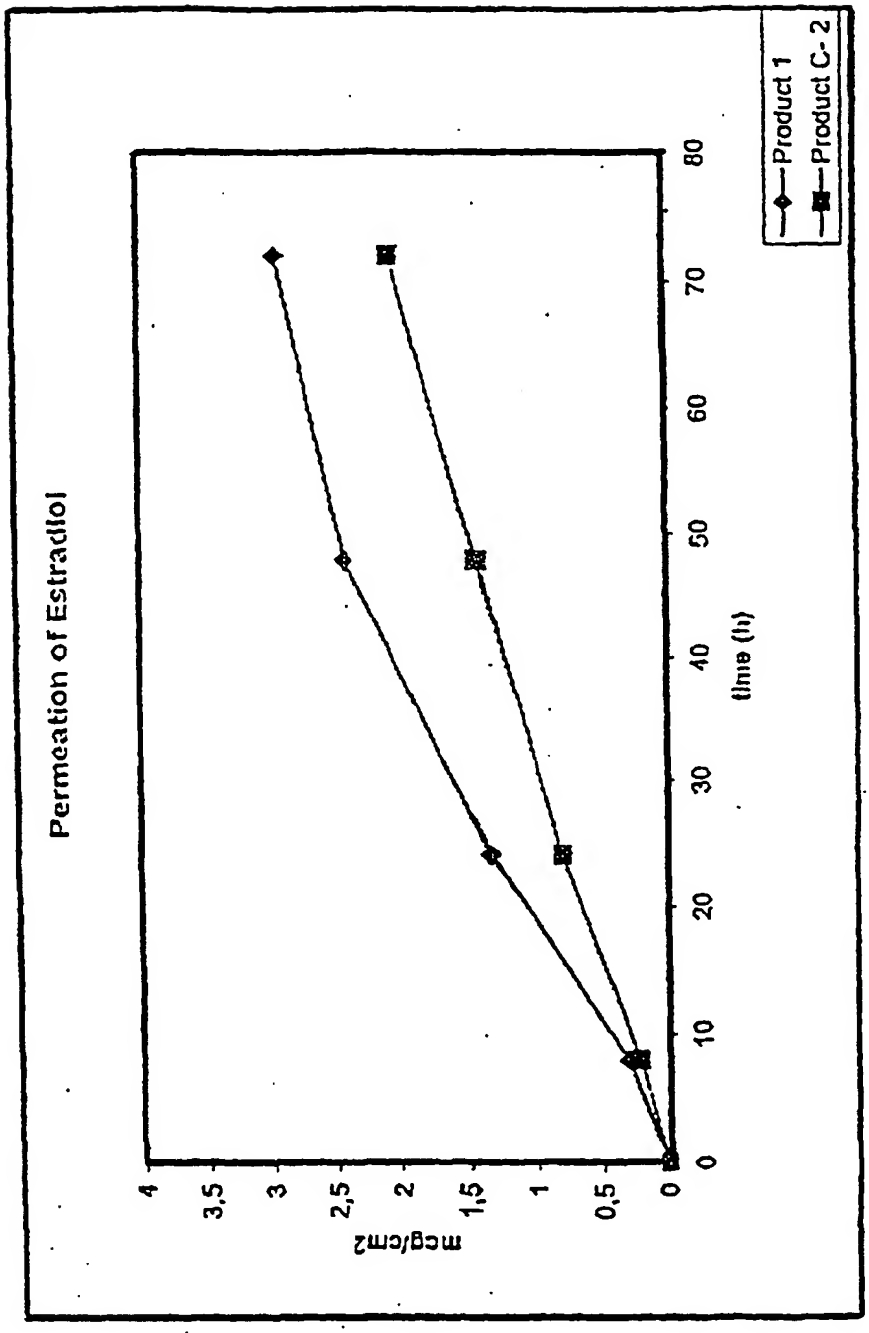


Fig. 4: Flux of Estradiol obtained from TDDS manufactured using the present invention

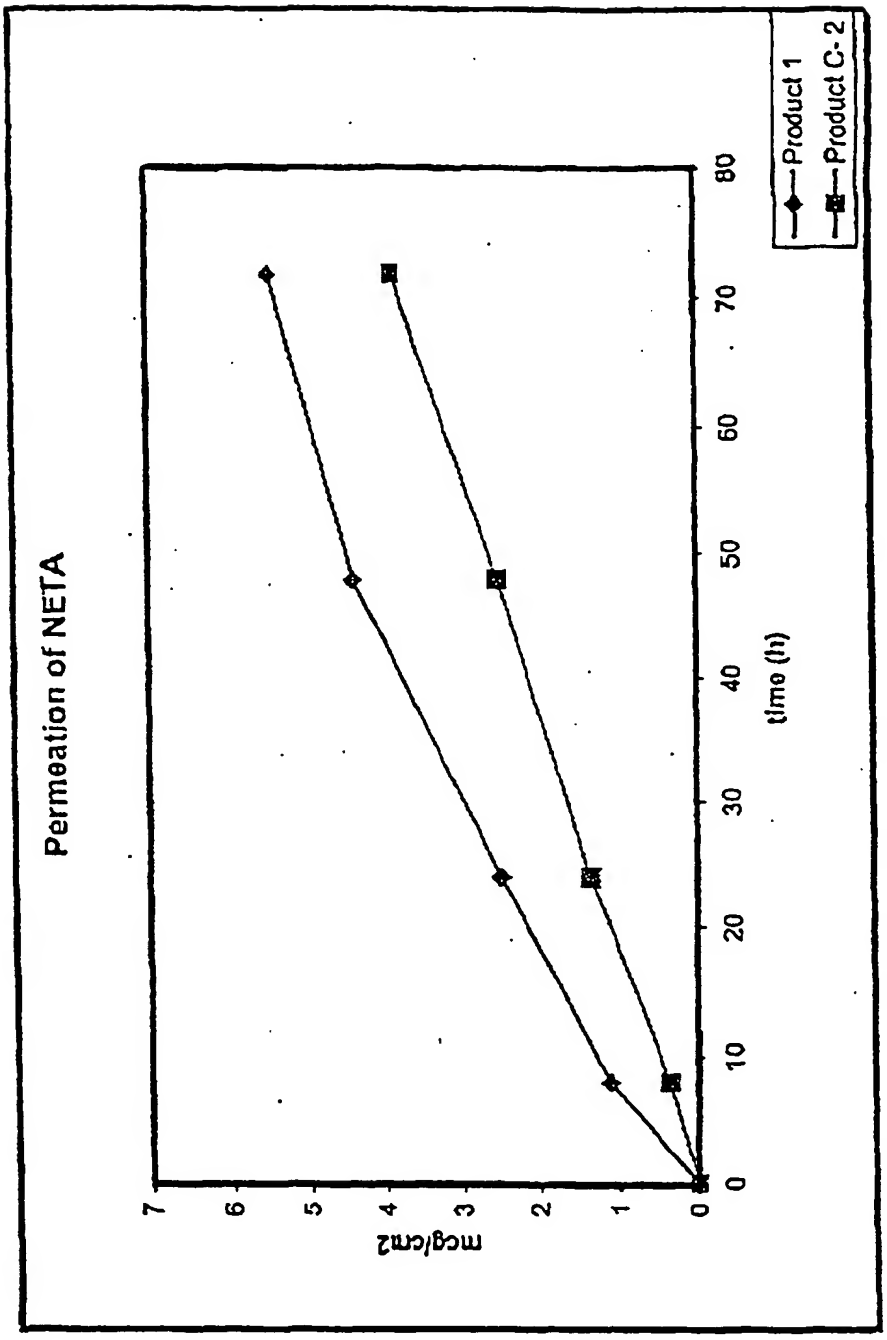


Fig. 5: Flux of NETA obtained from TDDS manufactured using the present invention

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(54) MATRIX-TYPE TRANSDERMAL PATCH FOR STEROID HORMONES

TRANSDERMALES PFLASTER DES MATRIXTYPS FÜR STEROIDHORMONE

TIMBRE TRANSDERMIQUE, DU TYPE MATRICE, DESTINE A DES HORMONES STEROIDES

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Description

[0001] The present invention relates to a Transdermal Drug Delivery System (TDDS) (a transdermal patch), to a method for manufacturing such system, and to the use of such system for hormone replacement therapy.

[0002] Estrogens are hormones which are necessary for the sexual development of females at puberty and for the maintenance of the oestrous cycle and secondary sexual characteristics. Estrogens and progesterone induce changes in the reproductive tract and elsewhere in the body of females during the menstrual cycle. Blood estrogen concentrations must be above a certain level for the maintenance of both proliferate and (together with progesterone) secretory phases of the uterine endothelium.

[0003] The menopause occurs when menstruation ceases and indicates the end of a woman's reproductive life; during this phase of a woman's life there is a progressive loss of ovarian functions and there is a decrease in the production of Estradiol and other hormones.

[0004] About 40% of women develop menopausal symptoms serious enough to require medical treatment; the symptoms include mainly vasomotor instability (hot flushes and sweating) and mood and sleep disturbances; during menopause, there is a gradual decrease of bone mass due to a loss of the modulating effect of Estradiol on bone resorption and this process normally leads to osteoporosis. The loss of estrogenic activity changes also the lipid metabolism with a decrease of the ratio of high density lipoprotein (HDL) to low-density lipoprotein (LDL), and this change increases the risk of cardiovascular diseases.

[0005] All these negative effects that can occur in a woman in menopause can be eliminated or at least reduced by an appropriate replacement therapy with estrogen agents, i.e. by the "Hormonal Replacement Therapy" (HRT).

[0006] Oral administration of estrogens as HRT has been extensively used for about 30 years and it was confirmed that, besides the climacteric symptoms, HRT was effective in reducing the death by cardiovascular diseases.

[0007] However, although oral estrogens are effective as HRT, related adverse effects are a problem; a high amount (60 - 90%) of the oral estrogens are converted within the gut wall and liver to inactive metabolites having hepatic adverse effects, therefore relatively high doses of oral estrogens are required to compensate first-pass metabolism.

[0008] Several non-oral formulations of estrogens, which avoid hepatic first-pass effects, have been developed and used as HRT; they include subcutaneous implants, intramuscular injections, vaginal creams and percutaneous gels. However, with such preparations, control of dosage is difficult and patients compliance is poor.

[0009] More recently, transdermal preparations delivering Estradiol at a constant rate have become available. In women with an intact uterus estrogens produce hypertrophy of the endometrium which could provoke cancer. In order to minimize the risk of endometrial hyperplasia and carcinoma of the estrogen therapy in women with an intact uterus the treatment must be opposed intermittently by a progestogen to be associated to the estrogen. The opposition therapy normally is carried out by oral administration of a progestogen like medroxyprogesterone acetate, norethindrone, norethindrone acetate, progesterone, etc. for 10 - 14 days per month.

[0010] A patch delivering both Estradiol and a progestogen is an useful alternative to a method which combines the transdermal administration of Estradiol with the daily oral administration of progestogen. Compliance is likely to be further improved and side effects minimized thanks to a lower progestogen dosage requirement compared with oral therapy.

[0011] Several problems, however, are encountered when including a progestogen in a transdermal patch. Among these one important obstacle is the low, therapeutically uneffective drug release obtained with a transdermal patch of relatively small size; this is due to the poor skin permeation properties of steroid hormones. Another obstacle is the low stability of some progestogens that leads to degradation products.

[0012] In the light of the aforementioned art, there is a need for an optimal transdermal drug delivery system releasing Estradiol and a progestogen through an intact skin resulting in a constant systemic absorption rate.

[0013] Numerous patents refer to the delivery of steroid hormones to the systemic circulation via a transdermal route, and some of them refer to transdermal systems containing Estradiol and Norethindrone Acetate.

[0014] Some inventions refer to the discovery of special matrix formulations containing substances able to reduce the re-crystallization of Estradiol and Norethindrone. Indeed, it is well known for scientists skilled in TDDS that, in order to obtain an adequate release of steroid hormones from transdermal patches, it is necessary to reach in the matrix high concentrations of the hormones (high drug load) or to significantly increase the release area of the patch. The first solution, however, leads quite often to re-crystallization of the hormones during the shelf-life of the product with consequent reduction of the drug release; the second solution often is not acceptable since it reduces patient compliance because of the size of the patch and even could have a negative effect on the adhesivity of the patch during the intended period of use of the product.

[0015] A third possibility to reach an adequate flux from matrix transdermal patches is the inclusion of absorption enhancers (penetration enhancers) in the matrix formulation to generate a high flux of the active compounds when the system is applied to the skin. Typical known enhancers are ethanol, glycerolmonolaurate, DMF, polyethylenglycole monolaurate, etc. Absorption enhancers, however, provoke skin reactions and systemic side effects and this aspect

reduces the ratio efficacy/tolerability of the resulting transdermal systems. They increase the permeability of the stratum corneum of the skin through a modification of the cellular layer, provoking lesions of the skin; they can moreover be absorbed by the skin provoking systemic side effects.

[0016] Another problem known by skilled researchers in TDDS formulations is the low stability of Norethindrone Acetate in acrylic based formulations that leads to degradation products.

[0017] WO 96/03119 (PCT/EP 95/02938) relates to a device for the administration of Estradiol alone or in combination with progestogen(s), encompassing a specific penetration enhancer that achieves elevated transdermal fluxes and optionally an anti-oxidant that achieves good product stability; however, as mentioned above, penetration enhancers can provoke skin reactions.

[0018] WO 94/23707 (PCT EP 94/01231) describes an active substance containing laminated plasters with a carrier and a matrix made of one or two polymers, as well as Vitamin E (tocoferol); tocoferol, however, is not free of potential skin reactions in an occlusive patch that has to remain attached to patient skin for 3-4 days.

[0019] US Patent 4,379,454 refers to a transdermal liquid reservoir patch which contains Estradiol in an alcoholic gel solution; the alcohol contained in the reservoir, however, acts also as an absorption enhancer and can provoke skin reactions.

[0020] WO 9740792 A discloses a matrix type patch for transdermally administering a steroid hormone which comprises a skin permeation enhancing amount of a diethanolamide of a 12 - 18 C fatty acid.

[0021] WO 95/09618 (PCT/EP 94/03269) describes the use of octyldodecanol as crystallization inhibitor in matrix patches containing Estradiol and Norethindrone Acetate.

[0022] DE 44 29 664 refers to a transdermal therapeutic system containing Estradiol and a water absorbing additiv, which is part of the matrix. The system according to this document does not contain a progestogen agent and is said to be applicable to Estradiol only.

[0023] A system for the application of norethisterone acetate is disclosed in DE 195 48 332. It is, however, stated in this document that the addition of an Aerosil to a matrix does not result in a reduced formation of degradation products of norethisterone acetate.

[0024] The object of the invention is the development of a TDDS for HRT releasing Estradiol and at least one progestogen with improved skin permeation of the hormones compared to prior art.

[0025] At the same time the TDDS is to have the following characteristics:

- very simple composition and structure;
- absence of skin penetration enhancers or other compounds which can irritate the skin;
- prolonged and controlled rate of release of the hormones up to 7-days;
- small size;
- good adhesivity onto the skin during the intended period of use;
- easy removal from the skin at the end of the treatment;
- "skin-safe" pressure sensitive adhesive;
- absence of re-crystallization of Estradiol and of the progestogen;
- stability of Estradiol and Norethindrone Acetate without degradation products;
- transparent, cosmetically attractive system;
- good physical stability, i.e. small tendency of creeping of the matrix so that the system can easily be removed from the package.

[0026] It has now been found that it is possible to obtain a TDDS containing steroid hormones that can release high amounts of hormones from relatively small matrix areas without the use of penetration enhancers and avoiding the recrystallization and the degradation of the hormones in the matrix and satisfying all the above characteristics.

[0027] Thus the present invention provides a transdermal patch for the release of Estradiol and at least one progestogen agent through the skin, comprising or consisting of an outer backing foil, a matrix and a protective liner wherein the Estradiol and the progestogen agent(s) are present in the matrix in an over saturated solution, the matrix contains 1 to 5, preferably 1 to 4 wt-% activated SiO_2 and the matrix has a moisture content of less than 0.7 wt.-%. Preferably the matrix has a moisture content of less than 0.5 wt-% and especially preferred is a moisture content of less than 0.4 wt-%. The moisture content refers to the content of free water, that is, the water not adsorbed on or absorbed in the SiO_2.

[0028] In the description and in the claims all percentages refer to weight-% if not indicated otherwise and all contents of the matrix, given in percentages, refer to the weight of the final matrix in the patch, that is, the matrix which comprises the copolymer(s), estradiol, the progestogen agent(s) and optionally further compounds.

[0029] Surprisingly it was found that the hormone release rate from such "moisture-free" matrix-type TDDS containing activated SiO_2 increases significantly with reference to the same non moisture free matrix without using penetration enhancers:

[0030] It was found that moisture-free semi-solid matrix-type TDDS which contain ativated silicon dioxide and steroid hormones in over-saturated solutions have an optimal performance with reference to the release rates of such steroid hormones when applied to human skin. Such unexpected behaviour, although not known with certainty and without intention to be bound to any specific mechanism, is believed to be due to absorption of water from the skin, especially by activated silicon dioxide, when such moisture-free activated silicon dioxide containing systems are applied to human skin and to the consequent decrease of the solubility of the hormones in the matrix. This provokes an increase of the driving force in the system and therefore results in a better flux of the drugs (such surprising characteristics of a matrix containing non water-soluble polymers were not known). It is therefore possible to have a high release of the hormones with TDDS of small release areas (and/or reduced concentration of hormones).

[0031] Moisture-free matrix systems can be obtained by standard manufacturing TDDS processes and concomitant or subsequent treatment of the systems with infrared rays. Thus the energy of water molecules is activated provoking the evaporation of residual water from the matrix at relatively low temperatures that do not provoke degradation of the steroid hormones.

[0032] Moisture-free matrix TDDS which contain activated silicon dioxide in the matrix show an enhanced drug release into the skin. Such surprising indirect enhancing properties in TDDS of moisture-free matrix TDDS containing activated silicon dioxide for steroid hormones were not previously known. In this invention the high rate of delivery is due to a different mechanism compared to that of penetration enhancers utilized in TDDS:

[0033] It is assumed that activated SiO_2 enhances the flux of water from the skin into the matrix thereby increasing the force which drives the hormones out of the matrix so that the flux of Estradiol and the progestogen agent(s) into the skin is/are increased.

[0034] It has been found that a preferred amount of SiO_2 in the matrix lies in the range from 2.5 to 3.5 wt-%; and an amount of about 3 wt-% SiO_2 is especially preferred. An amount above 5 wt-% is detrimental to the flux of the active ingredients in the matrix in that the concentration of the ingredients in the matrix must be lowered when the content of SiO_2 is increased. An amount of less than 1 wt-% SiO_2 will not attract a sufficient amount of water to increase the flux of the active ingredients.

[0035] SiO_2 can be activated according to the present invention by irradiating the patch - with or preferably without the release liner being applied - with an IR-source. At the same time irradiation of the matrix reduces its water content to the required level.

[0036] The matrix systems according to the present invention can thus be obtained by standard manufacturing TDDS processes and concomitant or subsequent treatment of the systems with infrared rays.

[0037] By irradiation the energy of water molecules is probably activated provoking the evaporation of residual water from the matrix and inter alia the evaporation of absorbed water of SiO_2 at relatively low temperatures.

[0038] Activated silicon dioxide can be prepared by irradiating silicon dioxide (like an Aerosil, especially Aerosil 380) with an IR source.

[0039] It has been shown that the results are particularly adequate when irradiating the matrix of the patch including the silicon dioxide with infrared rays having a wavelength of 1 to 100 µm, preferably of 1 and 10 µm, for 1 to 10 minutes, preferably for 1 to 5 minutes with an incandescent filament lamp of an adequate power (Watt) at a distance of 20 to 40 cm generating a temperature of 40 to 120 °C, preferably of 60 to 90 °C. Preferably the lamp(s) have an active power of 100 to 3000 Watt.

[0040] The inclusion in the matrix of activated, preferably colloidal, silicon dioxide moreover contributes to maintain the system anhydrous. This condition of the matrix system probably reduces the solubility of the hormones in the patch and increases the flux.

[0041] The most important feature of this invention is the use of a moisture-free matrix containing activated silicon dioxide which allows for a high flux of drugs into the skin from small patches without skin penetration (rate) enhancers.

[0042] The at least one pressure sensitive adhesive used for the matrix of this invention is selected from a group of vinylacetate containing acrylate copolymers; specifically the matrix consists of one, two or more pressure sensitive adhesive copolymers, obtainable by the radical copolymerisation of:

a) 2-ethylhexylacrylate (2-EHA) preferably in an amount of 44% to 80%, preferably 48% to 75% and especially 50% to 68%.
b) Hydroxyethyl-acrylate (HEA) preferably in an amount of 2.5% and 9.7%, preferably 4.0% to 5.0%;
c) vinylacetate (VA) preferably in an amount of 8% to 48.2%, preferably 20% to 26%;
d) glycidylmethacylate (GMA), preferably in an amount of 0.01 to 0.3%, preferably of 0.1% to 0.2%;
e) and in the presence of other substances in quantities of up to 5%, all percentages being based on the weight of the matrix of the final patch.

[0043] Among several progestogens, Norethindrone Acetate is preferred because it is effective at low doses and therefore can be formulated in TDDS and because it has some additional effects, e.g. on libido, that are absent in other

progestogens like progesterone and medroxyprogesterone.

[0044] In the described matrix Estradiol (as hemihydrate) and the progestogen agent(s) like Norethindrone Acetate can be maintained in high concentration. Thus the matrix can have an Estradiol content of 1.0 to 3%, preferably of 1.5 to 2.5 % and especially of 1,8 to 2.4% and a content of at least one progestogen agent like Norethindrone Acetate of 2 to 12%, preferably of 4 to 11% and especially of 5 to 9%. In these concentrations, Estradiol and the progestogen agent like Norethindrone Acetate, although being in a supersaturated (= over saturated) solid solution in this matrix, do not re-crystallize and are maintained in a condition that confers to the steroid hormones a high thermodynamic activity.

[0045] The matrix can preferably contain 1 to 5 wt-% of silicon dioxide to contribute to the maintanance of an anhydrous state in the matrix and to provoke absorption of water from the skin when the patch is applied.

[0046] In order to eventually improve the matrix characteristics, it is possible to include in the matrix small amounts of up to 4%, preferably of up to 3 % of other compounds having e.g. a solubilizing effect on the active ingredients, or avoiding re-crystallization thereof or having drying activities or acting as preservatives or antioxidants, etc.

[0047] Preferably the thickness of the matrix should be kept low enough so that it can be dried during the drying step of the manufacturing process and that the solvent content, including the moisture content can be reduced to a minimum.

[0048] Thus the matrix preferably has a thickness of 20 to 100 μm, more preferred of 30 (or 40) to 80 μm and especially of 50 to 70 μm.

[0049] The patch according to the present invention can be a laminated composite with a backing foil that is substantially impermeable to the drugs and the adhesive copolymer(s) of the matrix and supports the matrix.

[0050] The backing foil can be made from one or more materials selected from the group consisting of polyester, polyurethane, polyethylene, polyethylene terephtalate, polypropylene and polyvinyl chloride materials; and the side of the backing foil not facing the matrix can be lacquered, preferably by a lacquer comprising epoxy resins or polyaminoamido resins containing opacifying agents and it can have a thickness of 10 to 45 (or 50) μm and preferably 12 (or 15) to 30 μm.

[0051] Thus the backing foil or layer according to the present invention can be an occlusive or a transparent material, preferably a transparent polyester material such as polyethylene terephthalate.

[0052] For better handling during its production such material can be lacquered on the side not in contact with the matrix with an epoxy resin containing opacifying agents.

[0053] In order to protect the matrix during storage a protective (release) liner is used; such release liner can be impermeable to the active ingredients and the pressure sensitive adhesive(s) and should be easily removable by the patient before the application of the patch.

[0054] The release liner can be made of at least one foil of paper, polyester, polyethylene, polypropylene, polyethylene terephtalate (PET) or polyvinylchloride. It is preferably coated, to reach the requested release strength, on one or both sides with a silicon system or fluoropolymer coating blend. The optimum thickness for an appropriate rigidity of the release liner is 50 to 150 (or 200) μm and preferably between 60 (or 80) to 120 (or 150) μm.

[0055] In order to facilitate its detachment from the patch, a pull-off tag can be cut in the release liner and, where requested, an appropriate profile ring is stamped on the liner in order to maintain a distance from the backing foil to the internal wall of a pouch (sachet) material into which the patch can be sealed, so that the profile ring prevents the sticking of the patch on the internal wall of the sachets. The sachet can comprise a humidity impermeable foil, preferably a multi-layered foil, which is preferably made of sheets of aluminium, paper, polyethylene or polyvinylchloride, especially Surlyn^{R}.

[0056] To maintain the matrix "moisture-free" (to allow a high flux of the hormones) the sachets can contain as a precaution a desiccant such as silica gel, sodium sulfate, calcium sulfate, calcium carbonate dihydrate or a mixture thereof.

[0057] Preferably the transdermal patch according to the invention has a circular or oval shape or a square shape with round edges, and/or a release area of 5 to 60 cm^2 and preferably 8 to 40 cm^2.

[0058] According to the present invention there is also disclosed the use of a transdermal patch according to the invention for hormonal replacement therapy.

Examples

[0059] The description of the present invention and the manufacture of the relevant TDDS delivering Estradiol and a progestogen agent like Norethindrone Acetate are illustrated by the following examples:

Example 1

Preparation of the adhesive mixture with ingredients:

[0060] 12.05 kg of a vinylacetate-acrylate copolymer solution having a solid content of about 51% are homogenized under stirring together with 0.1621 kg of Estradiol Hemihydrate and 0.6055 kg of Norethindrone Acetate; the suspension is transferred into 6.96 kg of a 50 : 50 mixture of Ethyl Acetate and Ethanol (these solvent materials were later removed during drying) and 0.2098 kg of Aerosil 380 are added; the mixture is then maintained under stirring for 24 hours at room temperature until a homogenous mass is obtained.

[0061] The ratio of the monomers used to prepare the vinylacetate-acrylate copolymer of the (final) matrix obtained are as follows:

- 2-ethylhexyl acrylate: 58.67 %
- vinylacetate: 22.43 %
- 2-hydroxyethylacrilate: 4.31 %
- glycidyl metacrylate: 0.13 %

Preparation of the medicated laminate:

[0062] The drug solvent polymer mixture was then cast to a thickness of about 60 micrometers on a polyester film (backing foil) to obtain after drying a matrix having a weight of 60 g/m^2.

[0063] Drying of the medicated laminate is carried out at a temperature between 35 and 95°C and this leads to a composition of 0.135 mg of Estradiol and 0.520 mg of Norethindrone Acetate per cm^2 of the dried matrix.

[0064] At this temperature the matrix cannot be dried completely and the water content deriving from the materials and solvents used, from the environment and also from the Estradiol Hemihydrate used cannot be eliminated. The medicated laminate, after drying, is treated for about 2 minutes with an IR lamp able to eliminate the water and to activate the silicon dioxide at a temperature of less than 100 °C. In this way it is possible to avoid degradation of the hormones and especially of Norethindrone Acetate that can occur if the matrix is treated at high temperatures.

[0065] After drying and IR lamp treatment, the release liner , i.e. a polyester foil of 80 µm thickness, coated with a fluoropolymer, is stuck on the matrix to form the final medicated laminate.

Punching of the transdermal patch:

[0066] Circular or oval shapes or square shapes with round edges having a release area of 8 to 40 cm^2 are punched from the medicated foil to form the final transdermal patches; the size is decided according to the requested release rate of Estradiol and Norethindrone Acetate.

[0067] A not-to-scale cross-sectional view and a front view of a transdermal patch obtained according to this invention is given in Figure 1.

[0068] In Figur 1

(1) is a lacquered backing foil
(2) is a drug containing adhesive matrix
(3) is a protective liner, and
(4) is a profile ring.

Sealing into the pouches:

[0069] Each transdermal patch is sealed into a pouch not permeable to moisture and composed of a 4-layered material made by paper, polyethylene foil, aluminium foil and surlyn ionomer foil. To maintain the matrix of the TDDS moisture-free, a desiccant like calcium carbonate dihydrate may be included in the pouch.

Comparative Example 2 (reference preparation)

Preparation of the medicated laminate:

[0070] Proceed as in Example 1.

[0071] All the remaining steps are as in Example 1; in this example, however, the medicated laminate is not irradiated with the infrared lamp(s).

Quantitative assay of (free) water in transdermal patches

[0072] The transdermal patches resulting from each of the preparations described have been tested with the Karl-Fischer method in order to quantify the (free) water content in the matrix of the systems:

[0073] The (free) water content in the transdermal patches can be driven off in a tube furnace at a certain temperature. It can then be transferred to a Karl-Fischer titration cell by an inert gas where it is titrated by a Coulometric method with specific reagents. A suitable arrangement for such a technique is depicted in Figure 2.

[0074] A constant flow of air is achieved by regulating valve R and monitoring the air flow using the flowmeter D. The air is then dried in the drying towers T before being passed over the heated sample (P) (a patch or portion of patch) into the titration cell Z depicted in Figure 3.

[0075] In Figure 3

(1) is an inner burette,
(2) is a catholyte,
(3) is a cathode,
(4) is a membrane,
(5) is an anode,
(6) is a detection electrode (double platinum pin electrode),
(7) is a titration vessel,
(8) is an anolyte, and
(9) is a rotor.

[0076] In this assay the following devices, reagents and experimental conditions can be used:

1. Apparatus

The specific apparatus used is the METTLER DO 337 Drying Oven coupled with the METTLER DL 37 KF Coulometer.

2. Reagents used in the titration cell

- Hydranal® - Coulomat AG, art. 34836 (in compartment A)
- Hydranal® - Coulomat CG, art. 34840 (in compartment C) (supplier Riedel-de-Haën, D- 30918 Seelze, Germany)

3. Experimental conditions

The experimental conditions used for determining the (free) water content in the matrix of the transdermal patches were:

- Flow of air: 300 ml/min
- Temperature of the furnace: 80 °C
- Size of the patch sample: 20 cm^2
- Time of exposure of sample to 80 °C: 15 minutes

[0077] The system can detect from 100 to 3000 µg of (free) water equivalent to a percentage of water in the matrix of the present invention ranging approximately from 0.1 to 2.5 %.

[0078] With this system the content of (free) water in the matrix is determined, the amount of water adsorbed on or absorbed by the silicon dioxide cannot be determined thereby.

[0079] For each of the products according to the two examples five units have been tested and the results are shown below:

Table 1:

Moisture content in Estradiol - NETA patches		
Product	*1*	*C-2*
Moisture wt.-%	0.15	0.85
	0.13	0.81
	0.18	0.72
	0.15	0.78
	0.16	0.75
Average	0.15	0.78
SD	0.0013	0.0507

[0080] A comparative study of the flux trough human cadaver skin, carried out with the modified Franz diffusion cell, is presented in the following tables and graphs. It can be seen that the systems of the present invention exhibit elevated skin fluxes of Estradiol and Norethindrone Acetate (NETA) compared to the reference system.

Table 2 and Table 3: in-vitro release (human skin) of Estradiol and NETA

Cumulative mean value: release of Estradiol and NETA

Release of Estradiol (µg/cm^2, n=3)

Product	8 h	24 h	48 h	72 h	flux.µg/cm^2/h
1	0.310	1.319	2.412	2.932	0.049 s.d.±0.0071
C-2	0.217	0.797	1.424	2.054	0.031 s.d.±0.0021

Release of NETA (µg/cm^2, n=3)

Product	8 h	24 h	48 h	72 h	flux.µg/cm^2/h
1	1.118	2.482	4.395	5.481	0.090 s.d±0.0014
C-2	0.359	1.352	2.512	3.870	0.054 s.d±0.0020

Claims

1. A transdermal patch for the release of Estradiol and at least one progestogen agent through the skin, comprising or consisting of an outer backing foil, a matrix and a protective liner wherein

   a) the Estradiol and the progestogen agent(s) are present in the matrix in an oversaturated solution,
   b) the matrix contains 1 to 4 wt% activated SiO_2 , and
   c) the matrix has a moisture content of less than 0.7 wt.-%.

2. A transdermal patch according to claim 1 **characterized in that** the matrix has a moisture content of less than 0.5 wt.-%.

3. A transdermal patch according to claim 1 or 2, **characterized in that** the matrix contains 2,5 to 3,5 wt% SiO_2.

4. A transdermal patch according to any of the preceding claims **characterized in that** the SiO_2 is activated by irradiation with an infrared source.

5. A transdermal patch according to any of the preceding claims **characterized in that** it is free of penetration enhancers.

6. A transdermal patch according to any of the preceding claims **characterized in that** the matrix consists of one, two or more pressure sensitive adhesive copolymers obtainable by radical copolymerization of:

   - 2-ethylhexyl acrylate,
   - hydroxyethyl acrylate,
   - vinylacetate and
   - glycidyl methacrylate,

   optionally in the presence of **other substances** in quantities of up to 0.5 wt.-%, based on the weight of the matrix.

7. A transdermal patch according to claim 6 **characterized in that** the monomers are used in the following amounts:

   - 2-ethylhexyl acrylate is used in an amount of 44 to 80 wt.-%, preferably 48 to 75 wt.-% and especially 50 to 68 wt.-%,
   - hydroxyethyl acrylate is used in an amount of 2.5 to 9.7 wt.-%, preferably 4.0 to 5.0 wt.-%,
   - vinylacetate is used in an amount of 8 to 48.2 wt.-%, preferably 20 to 26 wt.-%, and
   - glycidyl methacrylate is used in an amount of 0.01 to 0.3 wt.-%, preferably 0.1 to 0.2 wt.-%, all percentages being based on the weight of the matrix.

8. A transdermal patch according to any of the preceding claims **characterized in that** the matrix has a thickness of 20 to 100 µm, preferably of 40 to 80 µm.

9. A transdermal patch according to any of the preceding claims, **characterized in that** the matrix has an Estradiol content of 1 to 3 wt.-%, preferably 1.5 to 2.5 wt.-% and especially 1.8 to 2.4 wt.-%.

10. A transdermal patch according to any of the preceding claims, **characterized in that** the matrix has a progestogen agent content of 2 to 12 wt.-%, preferably 4 to 11 wt.-% and especially 5 to 9 wt.-%.

11. A transdermal patch according to any of the preceding claims, **characterized in that** the matrix has a content of other compounds of up to 4 wt.-%.

12. A transdermal patch according to any of the preceding claims **characterized in that** the progestogen agent is norethindrone acetate.

13. A transdermal patch according to any of the preceding claims, **characterized in that**

- the backing foil consists of a material impermeable to the drugs and to the adhesive copolymer(s), preferably made from one or more materials selected from the group consisting of polyester, polyurethane, polyethylene, polyethylene terephtalate, polypropylene and polyvinyl chloride materials; and/or

- the side of the backing foil not facing the matrix is lacquered, preferably by a lacquer comprising epoxy resins and/or polyaminoamido resins containing opacifying agents and/or

- the backing foil has a thickness of 10 to 50 µm and preferably 12 to 30 µm.

14. A transdermal patch according to any of the preceding claims, **characterized in that** the patch comprises a removable protective liner

- made of at least one foil of paper, polyester, polyethylene, polyethylene terephtalate, polypropylene or polyvinylchloride or mixtures thereof, preferably coated with silicone or a fluoropolymer on one or both sides, and/or

- having a thickness of 50 to 200 µm and preferably 80 to 150 µm; and/or

- being provided with a cut-off tag and a stamped profile ring.

15. A transdermal patch according to any of the preceding claims, **characterized by** a circular or oval shape or a square shape with round edges, and/or a release area of 5 to 60 cm^2 and preferably 8 to 40 cm^2.

16. A transdermal patch according to any of the preceding claims, **characterized in that** it is sealed in a sachet comprising a humidity impermeable foil, preferably a multi-layered foil, which is preferably made of sheets of aluminium, paper, polyethylene or polyvinylchloride, especially ionomer foil.

17. A transdermal patch according to claim 16, **characterized in that** the sachet contains a desiccant like silica gel, sodium sulfate, calcium sulfate, calcium carbonate dihydrate or a mixture thereof.

18. A process for the production of a transdermal patch according to any of the preceding claims **characterized in that**

a) Estradiol and at least one progestogen agent are mixed with a copolymer solution,
b) a silicon dioxide is added to the mixture,
c) the mixture is applied to a backing layer to form a laminate,
d) the laminate is dried at a temperature from 35 to 95 °C,
e) the laminate is irradiated with IR-rays, and
f) the laminate is covered with a protective liner.

19. Use of a transdermal patch according to any of claims 1 to 17 for the manufacture of a medicament for hormonal replacement therapy.

Patentansprüche

1. Transdermales Pflaster für die Abgabe von Östradiol und mindestens eines gestagenen Mittels durch die Haut, umfassend oder bestehend aus einer äußeren Trägerfolie, einer Matrix und einer Schutzfolie, wobei

a) das Östradiol und das (die) gestagene(n) Mittel in der Matrix in einer übersättigten Lösung vorliegen,
b) die Matrix 1 bis 4 Gew.-% aktiviertes SiO_2 enthält, und
c) die Matrix einen Feuchtigkeitsgehalt von weniger als 0,7 Gew.-% besitzt.

2. Transdermales Pflaster nach Anspruch 1, **dadurch gekennzeichnet, daß** die Matrix einen Feuchtigkeitsgehalt von weniger als 0,5 Gew.-% besitzt.

3. Transdermales Pflaster nach Anspruch 1 oder 2, **dadurch gekennzeichnet, daß** die Matrix 2,5 bis 3,5 Gew.-% SiO_2 enthält.

4. Transdermales Pflaster nach einem der vorausgehenden Ansprüche, **dadurch gekennzeichnet, daß** das SiO_2

durch Bestrahlung mit einer Quelle für infrarote Strahlung aktiviert wird.

5. Transdermales Pflaster nach einem der vorausgehenden Ansprüche, **dadurch gekennzeichnet, daß** es frei von Penetrationsverstärkern ist.

6. Transdermales Pflaster nach einem der vorausgehenden Ansprüche, **dadurch gekennzeichnet, daß** die Matrix aus einem, zwei oder mehreren druckempfindlichen, klebenden Copolymeren besteht, erhältlich durch radikalische Copolymerisation von:

   - 2-Ethylhexyl-acrylat,
   - Hydroxyethyl-acrylat,
   - Vinylacetat und
   - Glycidyl-methacrylat,

   gegebenenfalls in Gegenwart von anderen Substanzen in Mengen von bis zu 0,5 Gew.-%, bezogen auf das Gewicht der Matrix.

7. Transdermales Pflaster nach Anspruch 6, **dadurch gekennzeichnet, daß** die Monomere in folgenden Mengen eingesetzt werden:

   - 2-Ethylhexyl-acrylat wird in einer Menge von 44 bis 80 Gew.-% verwendet, vorzugsweise 48 bis 75 Gew.-% und besonders 50 bis 68 Gew.-%,
   - Hydroxyethyl-acrylat wird in einer Menge von 2,5 bis 9,7 Gew.-% eingesetzt, vorzugsweise 4,0 bis 5,0 Gew.-%,
   - Vinylacetat wird in einer Menge von 8 bis 48,2 Gew.-% eingesetzt, vorzugsweise 20 bis 26 Gew.-%, und
   - Glycidyl-methacrylat wird in einer Menge von 0,01 bis 0,3 Gew.-% eingesetzt, vorzugsweise 0,1 bis 0,2 Gew.-%, alle Prozentangaben beziehen sich auf das Gewicht der Matrix.

8. Transdermales Pflaster nach einem der vorausgehenden Ansprüche, **dadurch gekennzeichnet, daß** die Matrix eine Dicke von 20 bis 100 µm besitzt, vorzugsweise von 40 bis 80 µm.

9. Transdermales Pflaster nach einem der vorausgehenden Ansprüche, **dadurch gekennzeichnet, daß** die Matrix einen Östradiolgehalt von 1 bis 3 Gew.-%, vorzugsweise von 1,5 bis 2,5 Gew.-%, und besonders von 1,8 bis 2,4 Gew.-% besitzt.

10. Transdermales Pflaster nach einem der vorausgehenden Ansprüche, **dadurch gekennzeichnet, daß** die Matrix einen Gehalt an einem gestagenen Mittel von 2 bis 12 Gew.-%, vorzugsweise von 4 bis 11 Gew.-%, und besonders von 5 bis 9 Gew.-% besitzt.

11. Transdermales Pflaster nach einem der vorausgehenden Ansprüche, **dadurch gekennzeichnet, daß** die Matrix einen Gehalt an weiteren Verbindungen von bis zu 4 Gew.-% besitzt.

12. Transdermales Pflaster nach einem der vorausgehenden Ansprüche, **dadurch gekennzeichnet, daß** das gestagene Mittel Norethindronacetat ist.

13. Transdermales Pflaster nach einem der vorausgehenden Ansprüche, **dadurch gekennzeichnet, daß**

   - die Trägerfolie aus einem Material besteht, das undurchlässig für die Arzneimittel und das (die) klebende(n) Copolymer(e) ist, vorzugsweise aus einem oder mehreren Materialien hergestellt ist, die aus der Gruppe ausgewählt werden, welche aus Polyester-, Polyurethan-, Polyethylen-, Polyethylenterephthalat-, Polypropylen- und Polyvinylchlorid-Materialien besteht; und/oder

   - die Seite der Trägerfolie, welche nicht der Matrix zugewandt ist, lackiert ist, vorzugsweise mit einem Lack, umfassend ein Epoxidharz und/oder Polyaminoamidoharze, die lichtundurchlässige Mittel enthalten, und/oder

   - die Trägerfolie eine Dicke von 10 bis 50 µm und vorzugsweise von 12 bis 30 µm besitzt.

14. Transdermales Pflaster nach einem der vorausgehenden Ansprüche, **dadurch gekennzeichnet, daß** das Pflaster eine abziehbare Schutzfolie umfaßt,

- welche aus mindestens einer Folie aus Papier, Polyester, Polyethylen, Polyethylenterephthalat, Polypropylen oder Polyvinylchlorid oder deren Mischungen besteht, vorzugsweise mit Silicon oder einem Fluorpolymer auf einer oder beiden Seiten beschichtet ist, und/oder
- eine Dicke von 50 bis 200 µm und vorzugsweise von 80 bis 150 µm besitzt; und/oder
- mit einem abgeschnittenen losen Ende und einem aufgeprägten Profilring versehen ist.

15. Transdermales Pflaster nach einem der vorausgehenden Ansprüche, **gekennzeichnet durch** eine kreisförmige oder ovale Form oder eine quadratische Form mit gerundeten Ecken und/oder einer Abgabefläche von 5 bis 60 cm^2, und vorzugsweise von 8 bis 40 cm^2.

16. Transdermales Pflaster nach einem der vorausgehenden Ansprüche, **dadurch gekennzeichnet, daß** es in einen Verpackungsbeutel eingeschlossen ist, umfassend eine feuchtigkeitsundurchlässige Folie, vorzugsweise eine multibeschichtete Folie, welche vorzugsweise aus Blättern von Aluminium, Papier, Polyethylen oder Polyvinylchlorid, insbesondere Ionomerfolien hergestellt ist.

17. Transdermales Pflaster nach Anspruch 16, **dadurch gekennzeichnet, daß** der Verpackungsbeutel ein Trocknungsmittel wie Silicagel, Natriumsulfat, Calciumsulfat, Calciumcarbonat-Dihydrat oder deren Mischungen enthält.

18. Verfahren zur Herstellung eines transdermalen Pflasters nach einem der vorausgehenden Ansprüche, **dadurch gekennzeichnet, daß**

    a) Östradiol und mindestens ein gestagenes Mittel mit einer Copolymerlösung vermischt werden,
    b) ein Siliciumdioxid zur Mischung hinzugegeben wird,
    c) die Mischung auf eine Trägerschicht aufgebracht wird, um eine Beschichtung zu bilden,
    d) die Beschichtung bei einer Temperatur von 35 bis 95° C getrocknet wird,
    e) die Beschichtung mit infraroten Strahlen bestrahlt wird, und
    f) die Beschichtung mit einer Schutzfolie bedeckt wird.

19. Verwendung eines transdermalen Pflasters nach einem der Ansprüche 1 bis 17 zur Herstellung eines Medikaments für die Hormonersatztherapie.

Revendications

1. Pansement transdermique pour la libération d'estradiol et d'au moins un agent progestogène à travers la peau, qui comprend ou qui est constituée d'une feuille de renforcement externe, d'une matrice et d'un revêtement protecteur, pansement pour lequelle:

    a) l'estradiol et le ou les agent(s) progestogènes sont présents dans la matrice sous la forme d'une solution sursaturée,

    b) la matrice contient 1 à 4 % en poids de SiO_2 activée, et

    c) la matrice a une teneur en humidité inférieure à 0,7 % en poids.

2. Pansement transdermique selon la revendication 1, **caractérisée en ce que** la matrice a une teneur en humidité inférieure à 0,5 % en poids.

3. Pansement transdermique selon la revendication 1 ou 2, **caractérisée en ce que** la matrice contient 2,5 à 3,5 % en poids de SiO_2.

4. Pansement transdermique selon l'une quelconque des revendications précédentes, **caractérisée en ce que** la silice SiO_2 est activée par exposition à une source de rayons infrarouges.

5. Pansement transdermique selon l'une quelconque des revendications précédentes, **caractérisée en ce qu'**elle est exempte d'agents facilitant la pénétration.

6. Pansement transdermique selon l'une quelconque des revendications précédentes, **caractérisée en ce que** la matrice est constituée d'un, de deux ou de plus de deux copolymères adhésifs sensibles à la pression, que l'on peut obtenir par copolymérisation radicalaire d'acrylate de 2-éthylhexyle, d'acrylate d'hydroxyéthyle, d'acétate de vinyle et de méthacrylate de glycidyle, éventuellement en présence d'autres substances en une proportion atteignant au plus 0,5 % en poids par rapport au poids de la matrice.

7. Pansement transdermique selon la revendication 6, **caractérisée en ce que** l'on utilise les monomères dans les proportions suivantes :

- l'acrylate de 2-éthylhexyle est utilisé en une proportion de 44 à 80 % en poids, de préférence de 48 à 75 % en poids et en particulier de 50 à 68 % en poids,
- l'acrylate d'hydroxyéthyle est utilisé en une proportion de 2,5 à 9,7 % en poids, de préférence de 4,0 à 5,0 % en poids,
- l'acétate de vinyle est utilisé en une proportion de 8 à 48,2 % en poids, de préférence de 20 à 26 % en poids, et
- le méthacrylate de glycidyle est utilisé en une proportion de 0,01 à 0,3 % en poids, de préférence de 0,1 A 0,2 % en poids,

tous les pourcentages étant basés sur le poids de la matrice.

8. Pansement transdermique selon l'une quelconque des revendications précédentes, **caractérisée en ce que** la matrice a une épaisseur de 20 à 100 µm, de préférence de 40 à 80 µm.

9. Pansement transdermique selon l'une quelconque des revendications précédentes, **caractérisée en ce que** la matrice a une teneur en estradiol de 1 à 3 % en poids, de préférence de 1,5 à 2,5 % en poids et en particulier de 1,8 à 2,4 % en poids.

10. Pansement transdermique selon l'une quelconque des revendications précédentes, **caractérisée en ce que** la matrice a une teneur en agent progestogène de 2 à 12 % en poids, de préférence de 4 à 11 % en poids et en particulier de 5 à 9 % en poids.

11. Pansement transdermique selon l'une quelconque des revendications précédentes, **caractérisée en ce que** la matrice a une teneur en autres composés de jusqu'à 4 % en poids.

12. Pansement transdermique selon l'une quelconque des revendications précédentes, **caractérisée en ce que** l'agent progestogène est l'acétate de noréthindrone.

13. Pansement transdermique selon l'une quelconque des revendications précédentes, **caractérisée en ce que**

- la feuille de renforcement est constituée d'une matière imperméable aux médicaments et aux copolymères adhésifs, faite de préférence d'un ou plusieurs produits choisis parmi les polyesters, les polyuréthanes, les polyéthylènes, les poly(téréphtalate d'éthylène), les polypropylènes et les polychlorures de vinyle, et/ou
- le côté de la feuille de renforcement qui ne fait pas face à la matrice, est laqué, de préférence au moyen d'une laque comprenant des résines époxy et/ou des résines polyaminoamido contenant des agents opacifiants, et/ou
- la feuille de renforcement a une épaisseur de 10 à 50 µm, de préférence de 12 à 30 µm.

14. Pansement transdermique selon l'une quelconque des revendications précédentes, **caractérisée en ce qu'**il comprend un revêtement protecteur ôtable, constitué d'au moins une feuille de papier, de polyester, de polyéthylène, de poly(téréphtalate d'éthylène), de polypropylène, de polychlorure de vinyle ou d'un mélange de ces produits, revêtue de préférence de silicone ou d'un polymère fluoré sur une face ou les deux faces, et/ou ayant une épaisseur de 50 à 200 µm, de préférence de 80 à 150 µm, et/ou muni d'une languette de détachage et d'un anneau à profil imprimé.

15. Pansement transdermique selon l'une quelconque des revendications précédentes, **caractérisée par** une forme circulaire, une forme ovale ou une forme carrée à angles arrondis, et/ou par une surface de libération de 5 à 60 cm^2. de préférence de 8 à 40 cm^2.

16. Pansement transdermique selon l'une quelconque des revendications précédentes, **caractérisée en ce qu'**elle est enfermée hermétiquement dans un sachet comprenant une feuille imperméable à l'humidité, de préférence une feuille multicouche, qui est constituée de préférence de feuilles d'aluminium, de papier, de polyéthylène, de poly(chlorure de vinyle) et en particulier d'ionomères.

17. Pansement transdermique selon la revendication 16, **caractérisée en ce que** le sachet contient un desséchant comme du gel de silice, du sulfate de sodium, du sulfate de calcium, du carbonate de calcium dihydraté ou un mélange de ces produits.

18. Procédé de production d'un pansement transdermique selon l'une quelconque des revendications précédentes, **caractérisé en ce que** :

a) on mélange de l'estradiol et au moins un agent progestogène à une solution de copolymère,

b) on ajoute du dioxyde de silicium au mélange,

c) on applique le mélange sur une couche de renforcement pour former un stratifié,

d) on sèche le stratifié à une température de 35 à 95 °C,

e) on irradie le stratifié avec des rayons infrarouges, et

f) on recouvre le stratifié avec un revêtement protecteur.

19. Utilisation d'un pansement transdermique selon l'une quelconque des revendications 1 à 17 pour la fabrication d'un médicament destiné à une thérapie de remplacement hormonal.

Fig. 1:

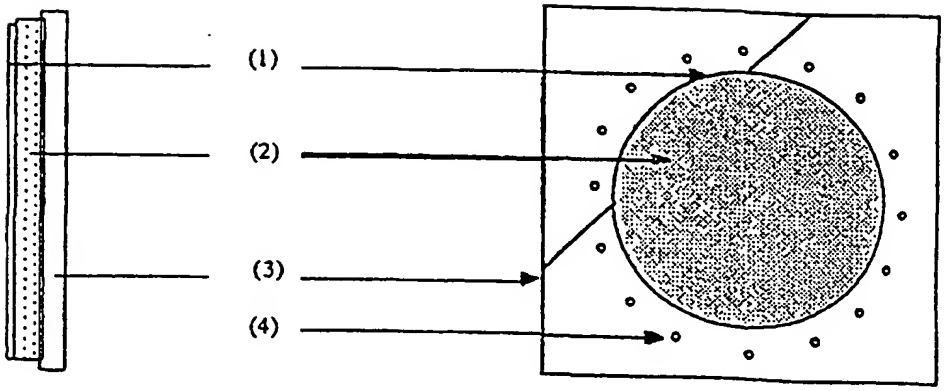
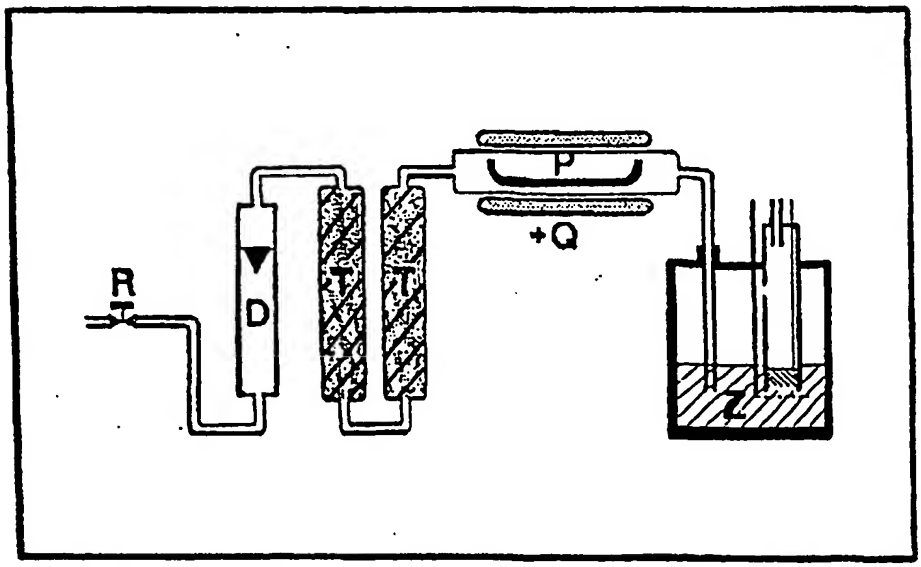


Fig. 2:



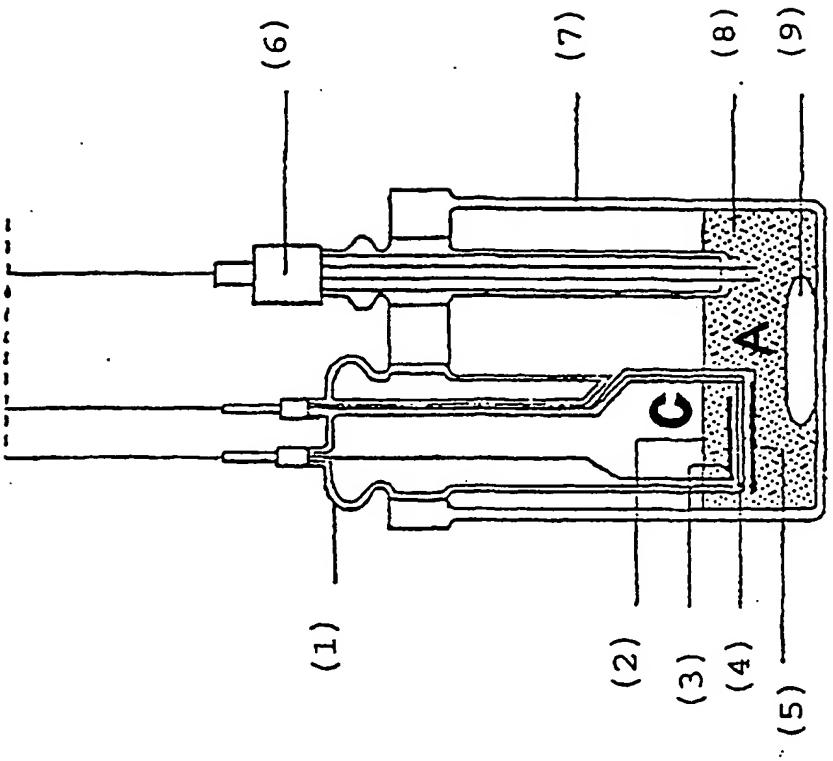


Fig. 3:

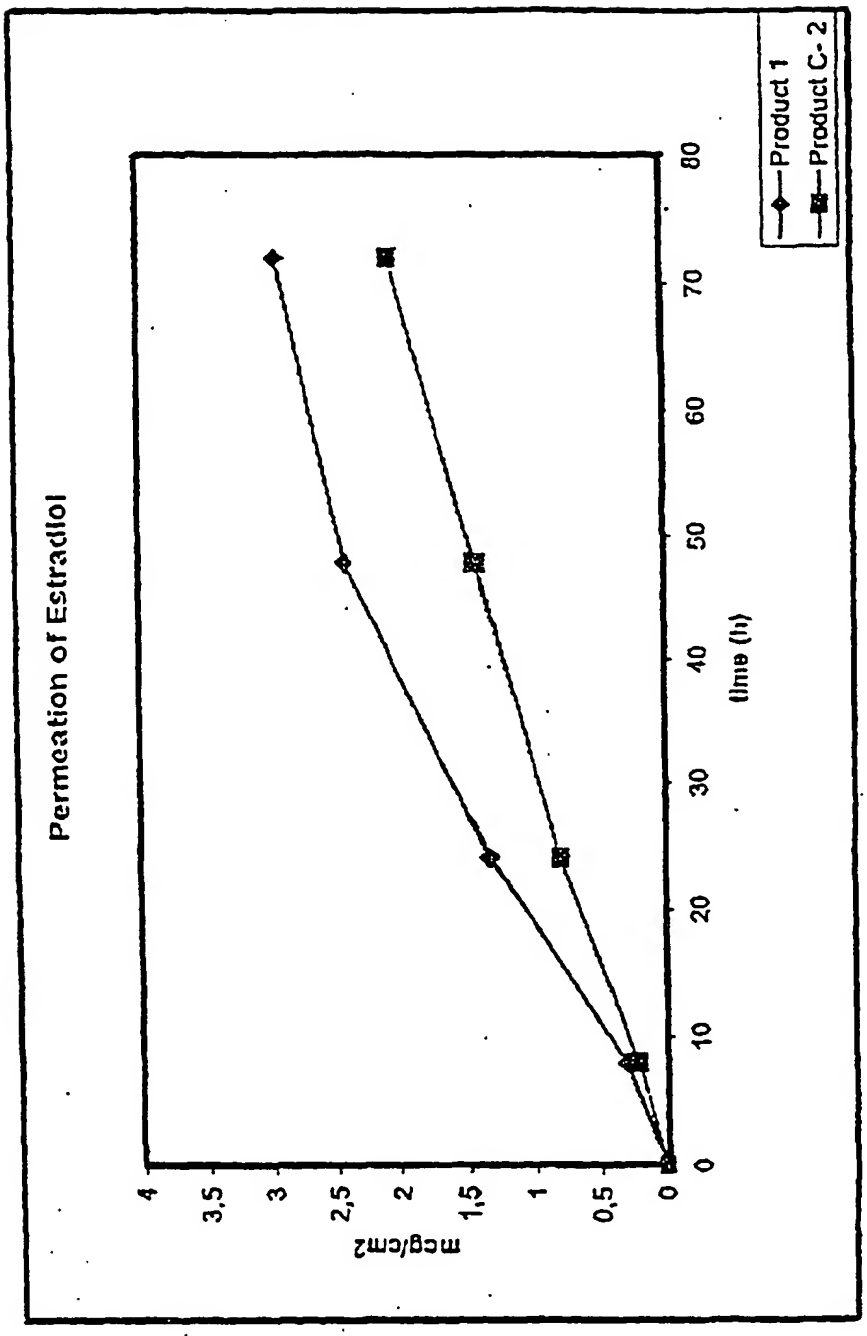


Fig. 4: Flux of Estradiol obtained from TDDS manufactured using the present invention

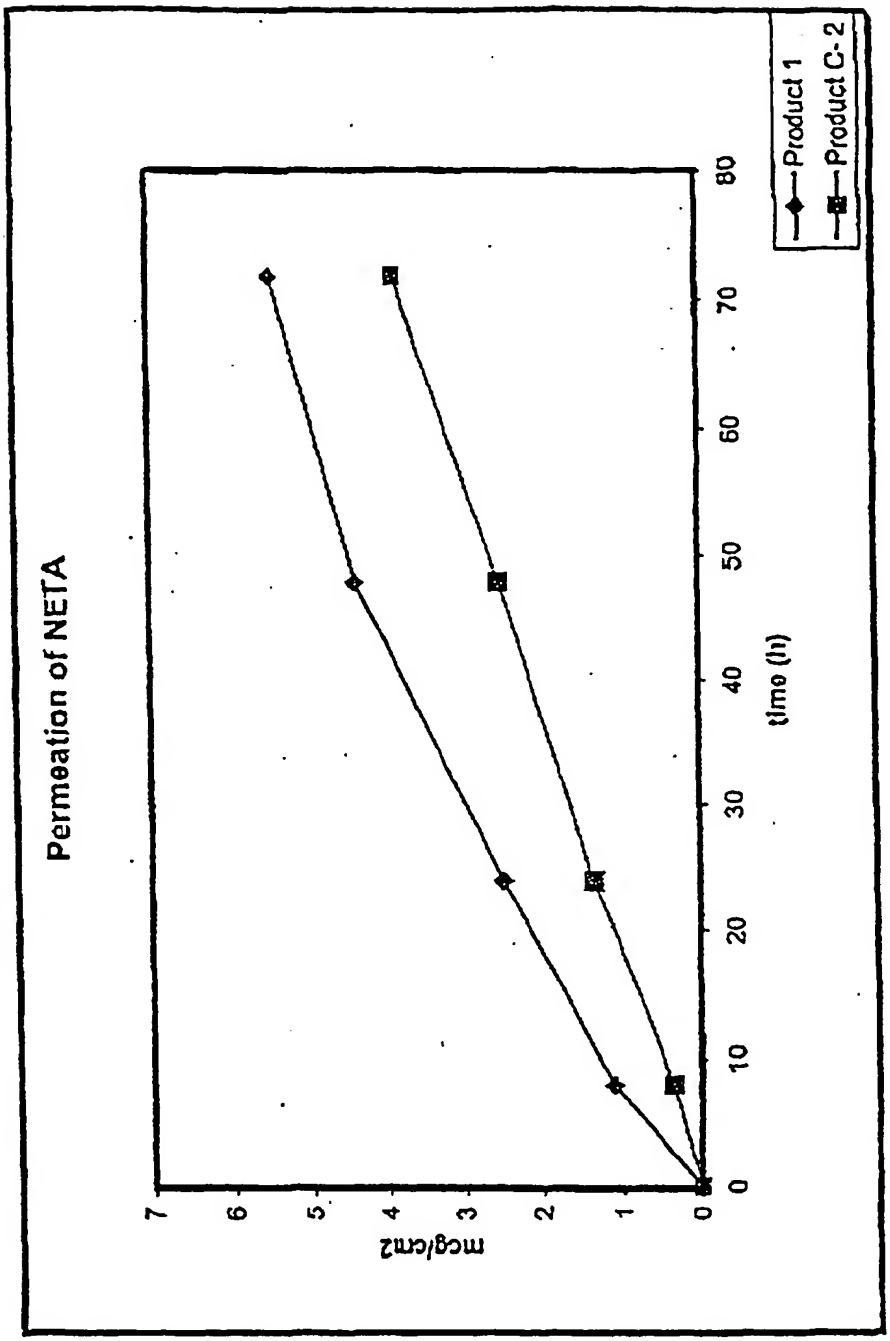


Fig. 5: Flux of NETA obtained from TDDS manufactured using the present invention